4000 Oral Abstract Session

Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer (EC/GEJC) following neoadjuvant chemoradiotherapy (CRT): First results of overall survival (OS) from CheckMate 577.

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Background: At 24.4-month (mo) median follow-up, adjuvant nivolumab demonstrated a statistically significant and clinically meaningful improvement in disease-free survival (DFS) vs placebo with a well-tolerated safety profile in patients (pts) with resected EC/GEJC with residual pathologic disease following neoadjuvant CRT and surgery in the primary analysis from the global, phase 3 CheckMate 577 study (NCT02743494). We report the final analysis of the hierarchically tested secondary endpoint of OS along with longer follow-up of DFS. **Methods:** Adults with resected (R0) stage II/III EC/GEJC who received neoadjuvant CRT and had residual pathologic disease were randomized 2:1 to nivolumab 240 mg or placebo Q2W for 16 weeks, followed by nivolumab 480 mg or placebo Q4W. Maximum treatment duration was 1 year. The primary endpoint was DFS. OS was a secondary endpoint, and exploratory endpoints included safety, distant metastasis-free survival (DMFS), and progression-free survival on subsequent systemic therapy (PFS2). **Results:** 794 pts were randomized (nivolumab, n = 532; placebo, n = 262). With a median follow-up of 78.3 (range, 60.1–96.6) mo, adjuvant nivolumab continued to show DFS benefit vs placebo (HR 0.76 [95% CI 0.63–0.91]; Table). Median OS was numerically longer with nivolumab vs placebo (51.7 vs 35.3 mo), although the difference was not statistically significant (HR 0.85 [95.87% CI 0.70–1.04]; *P* = 0.1064; Table). OS rates at 3 and 5 years with nivolumab vs placebo were 57% vs 50% and 46% vs 41%, respectively. OS subgroup analyses will be presented. Clinically meaningful improvement in DMFS with nivolumab vs placebo was maintained (Table). PFS2 favored nivolumab vs placebo (HR 0.81 [95% CI 0.67–0.98]). In the nivolumab group, 46% of pts received subsequent therapy vs 60% in the placebo group; 5% vs 15% received subsequent immunotherapy. No new safety signals were identified. **Conclusions:** Adjuvant nivolumab demonstrated sustained long-term DFS benefit and numerical improvement in OS vs placebo in pts with resected EC/GEJC and residual pathologic disease following neoadjuvant CRT. The safety profile of adjuvant nivolumab remained well-tolerated with longer follow-up. These results further support the use of adjuvant nivolumab in this pt population. Clinical trial information: NCT02743494. Research Sponsor: Bristol Myers Squibb.

Efficacy	Nivolumab (n = 532)	Placebo (n = 262)
Median DFS (95% CI), mo	21.8 (16.6–29.7)	10.8 (8.3–14.3)
HR (95% CI)	0.76 (0.63–0.91)	
Median OS (95% CI), mo	51.7 (41.0–61.6)	35.3 (30.7–48.8)
HR (95.87% CI; *P* value)	0.85 (0.70–1.04; *P* = 0.1064)	
Median DMFS (95% CI), mo	27.3 (21.4–36.0)	14.6 (10.9–20.3)
HR (95% CI)	0.75 (0.62–0.90)	
Safety, n (%)	**n = 532**	**n = 260**
Any-grade/grade 3–4 TRAEs	379 (71)/75 (14)	124 (48)/17 (7)
Any-grade/grade 3–4 TRAEs leading to discontinuation	48 (9)/26 (5)	8 (3)/7 (3)

TRAE, treatment-related adverse event.

4001 Oral Abstract Session

Lenvatinib plus pembrolizumab and chemotherapy versus chemotherapy in advanced, metastatic gastroesophageal adenocarcinoma: The phase 3, randomized LEAP-015 study.

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Background: LEAP-015 (NCT04662710), is a randomized, open-label, phase 3 study of pembrolizumab plus lenvatinib and chemotherapy as first-line treatment for advanced/ metastatic gastroesophageal adenocarcinoma. We report results from the interim and final analyses of LEAP-015. **Methods:** Eligible participants (pts) had untreated HER-2 negative locally advanced unresectable or metastatic gastroesophageal adenocarcinoma, measurable disease and ECOG PS 0-1. All pts were randomly assigned 1:1 to induction with pembrolizumab 400 mg IV Q6W (x2) plus oral lenvatinib 8 mg QD and investigators choice chemotherapy (CAPOX Q3W x4 or mFOLFOX6 Q2W x6) then consolidation with pembrolizumab 400 mg Q6W for ≤16 doses plus lenvatinib 20 mg QD (only if 8 mg tolerated for at least 3 weeks), or chemotherapy alone (CAPOX or FOLFOX). Randomization was stratified by region, ECOG PS, and chemotherapy choice. Dual primary endpoints were PFS (RECIST v1.1, BICR) and OS in pts with PD-L1 combined positive score (CPS) ≥1 and in all pts; secondary endpoints included ORR and DOR (RECIST v1.1, BICR) in pts with PD-L1 CPS ≥1 and in all pts, and safety and tolerability in all pts. The data cut-off date was Oct 29, 2024. **Results:** A total of 880 pts (78% PD-L1 CPS ≥1; 75% gastric primary) were randomized (443 pembrolizumab plus lenvatinib and chemotherapy; 437 chemotherapy alone).Median follow-up was 32.2 mo (range 19.0 – 41.7) in pts with PD-L1 CPS ≥1 and 31.8 mo (range, 19.0 – 41.7) in all pts. At interim analysis, PFS difference was statistically significant with pembrolizumab plus lenvatinib and chemotherapy vs chemotherapy in pts with PD-L1 CPS ≥1 (median 7.3 vs 6.9 mo; HR 0.75; 95% CI, 0.62-0.9; P = 0.0012), with 24-mo PFS of 20% vs 7%, and in all pts (median 7.2 vs 7.0 mo; HR 0.78; 95% CI, 0.66-0.92; P = 0.0019), with 24-mo PFS of 21% vs 8%. ORR was 59.5% vs 45.4% in pts with PD-L1 CPS ≥1 and 58.0% vs 43.9% in all pts; P < 0.0001 for both. At final analysis, OS in pts with PD-L1 CPS ≥1 was not statistically significant (median 12.6 vs 12.9 mo; HR 0.84; 95% CI, 0.71-1.00; P = 0.0244 (P-value boundary for significance of 0.0204), with 24-mo OS of 31% vs 23%. OS in all pts was not tested per multiplicity strategy (median 13.1 vs 13.0; HR 0.87; 95% CI 0.75-1.01). Drug-related adverse event (AE) rates were 98% vs 92% in pts receiving pembrolizumab plus lenvatinib and chemotherapy vs chemotherapy. Grade ≥3 drug-related AE rates were 65% vs 49% (grade 5 AEs 5% vs < 1%). **Conclusions:** Pembrolizumab plus lenvatinib and chemotherapy vs chemotherapy provided statistically significant improvement in PFS and ORR in pts with advanced unresectable or metastatic gastroesophageal carcinoma at interim analysis. However, there was no significant improvement in OS in pts with PD-L1 CPS ≥1 at final analysis. Safety profiles were consistent with known regimens, with higher AE rates seen in pts receiving the experimental treatment. Clinical trial information: NCT04662710. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA; N/A.

LBA4002 **Oral Abstract Session**

Trastuzumab deruxtecan (T-DXd) vs ramucirumab (RAM) + paclitaxel (PTX) in second-line treatment of patients (pts) with human epidermal growth factor receptor 2-positive (HER2+) unresectable/metastatic gastric cancer (GC) or gastroesophageal junction adenocarcinoma (GEJA): Primary analysis of the randomized, phase 3 DESTINY-Gastric04 study.

Kohei Shitara, Mahmut Gumus, Filippo Pietrantonio, Sara Lonardi, Christelle De La Fouchardiere, Clélia Coutzac, Jeroen Dekervel, Daniel Hochhauser, Lin Shen, Wasat Mansoor, Bo Liu, Lorenzo Fornaro, Min-Hee Ryu, Jeeyun Lee, Fabricio Souza, Lori Jukofsky, Yumin Zhao, Takahiro Kamio, Aziz Zaanan, Eric Van Cutsem; National Cancer Center Hospital East, Kashiwa, Japan; Istanbul Medeniyet University, Prof. Dr. Suleyman Yalcin City Hospital, Istanbul, Turkey; Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Veneto Institute of Oncology IOV, IRCCS, Padua, Italy; Centre Léon Bérard, Lyon, France; Department of Medical Oncology, Centre Léon-Bérard, Lyon, France; University Hospitals Gasthuisberg and University of Leuven, Leuven, Belgium; University College Hospital Macmillan Cancer Centre, London, United Kingdom; State Key Laboratory of Holistic Integrative Management of Gastrointestinal Cancers, Department of GI Oncology, Peking University Cancer Hospital & Institute, Beijing, China; Christie NHS Foundation Trust, Manchester, United Kingdom; Shandong Cancer Hospital, Jinan City, China; Azienda Ospedaliero Universitaria Pisana, Pisa, Italy; Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; Samsung Medical Center, Seoul, South Korea; Daiichi Sankyo, Inc., Basking Ridge, NJ; Hôpital Européen Georges Pompidou, Department of Digestive Oncology, Paris, France

4003 Oral Abstract Session

Claudin18.2-specific CAR T cells (Satri-cel) versus treatment of physician's choice (TPC) for previously treated advanced gastric or gastroesophageal junction cancer (G/GEJC): Primary results from a randomized, open-label, phase II trial (CT041-ST-01).

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Background: Claudin18.2 (CLDN18.2) has emerged as a promising therapeutic target in G/GEJC. Recently reported results showed CT041/satricabtagene autoleucel (satri-cel), an autologous CLDN18.2-specific CAR T-therapy, had encouraging efficacy in previously treated patients (pts) with advanced G/GEJC. Now we report the primary results from the phase II pivotal trial (CT041-ST-01, NCT04581473). **Methods:** In this open-label, multicenter, randomized controlled trial (RCT) conducted in China, CLDN18.2 positive, advanced G/GEJC pts with failure to at least 2 prior lines of treatment, were randomized (2:1) to satri-cel arm or TPC arm. For satri-cel arm, satri-cel dose of 250 $\times 10^6$ cells were infused up to 3 times. For TPC arm, one of the standard of care (SOC) drugs (apatinib, paclitaxel, docetaxel, irinotecan or nivolumab) was given per physician's decision. Those who experienced disease progression or drug intolerance in TPC arm could receive subsequent satri-cel, if eligible. The primary endpoint was PFS assessed by the Independent Review Committee (IRC). Key secondary endpoint was OS. Data cutoff date was Oct 18, 2024. **Results:** From Mar 29, 2022 to Aug 16, 2024, a total of 156 pts were randomized to satri-cel arm (n = 104) or TPC arm (n = 52). Twenty pts in TPC arm received subsequent satri-cel. Median number of prior systemic therapies was 2 in both arms, and 26.9% vs 19.2% had received ≥3 lines; 69.2% vs 59.6% had peritoneal metastasis; 71.2% vs 65.4% were Lauren diffuse/mixed type. The median follow-up time of PFS and OS was 8.90 and 12.29 months (m). In ITT population, satri-cel arm showed significant improvement in mPFS by IRC (3.25m vs 1.77m; HR 0.366, 95% CI: 0.241, 0.557; $p < 0.0001$) and an obvious trend for longer mOS (7.92m vs 5.49m; HR 0.693, 95% CI: 0.457, 1.051; one-sided p = 0.0416) than TPC arm. Moreover, in 136 pts receiving study drug (mITT, satri-cel 88 pts vs TPC 48 pts), mPFS by IRC was 4.37m vs 1.84m, HR 0.304 (95% CI: 0.195, 0.474) and mOS was 8.61m vs 5.49m, HR 0.601 (95% CI: 0.385, 0.939). Notably, mOS of TPC pts with satri-cel was 9.20m. Among all pts receiving satri-cel (n = 108) vs TPC pts without satri-cel (n = 28), mOS was 9.17m vs 3.98m, HR 0.288 (95% CI: 0.169, 0.492). A summary of study drug-related adverse events (TRAEs) is shown in the Table. **Conclusions:** This is the first confirmatory RCT of CAR T-therapy in solid tumors. Satri-cel demonstrated significant PFS improvement and an obvious OS benefit with a manageable safety profile. These results support satri-cel as a potential new SOC for advanced G/GEJC. Clinical trial information: NCT04581473. Research Sponsor: None.

Safety, n (%)	Satri-cel (n=88)	TPC (n=48)
TRAEs	88 (100)	44 (91.7)
Serious TRAEs	31 (35.2)	12 (25.0)
TRAE leading to death	1 (1.1)[a]	1 (2.1)[b]
CRS	84 (95.5)	0
Grade 1-2	80 (90.9)	0
Grade 3	4 (4.5)	0
ICANS	0	0

[a]disseminated intravascular coagulation;
[b]coagulopathy.

LBA4004 **Oral Abstract Session**

Results of a randomized phase III trial of pre-operative chemotherapy with mFOLFIRINOX or PAXG regimen for stage I-III pancreatic ductal adenocarcinoma.

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LBA4005 **Oral Abstract Session**

PANOVA-3: Phase 3 study of tumor treating fields (TTFields) with gemcitabine and nab-paclitaxel for locally advanced pancreatic ductal adenocarcinoma (LA-PAC).

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Preliminary results from the randomized phase 2 study (1801 part 3B) of elraglusib in combination with gemcitabine/nab-paclitaxel (GnP) versus GnP alone in patients (pts) with previously untreated metastatic pancreatic ductal adenocarcinoma (mPDAC).

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Background: Elraglusib (9-ING-41) is a first-in-class inhibitor of GSK-3ß, which may mediate drug resistance, EMT, and damaged DNA and tumor immune response in advanced cancer. In pancreatic cancer models in mice, elraglusib combined with chemotherapy enhanced anti-tumor effects and survival. In a single-arm clinical study, elraglusib/GnP showed antitumor activity and prolonged survival in pts with mPDAC. **Methods:** Pts with previously untreated mPDAC were randomized 2:1 to GnP plus elraglusib 9.3 mg/kg IV once weekly or GnP in an open-label phase 2 study. The primary endpoint was 1-yr OS in the primary analysis set. Upon study completion, mOS will be the primary endpoint once survival distributions are compared after the 12-month follow-up using log-rank analysis. Secondary endpoints included DCR, ORR, mPFS, and TEAEs/TRAEs. The planned sample size was 207 evaluable pts (130 for elraglusib/GnP and 77 for GnP), assuming 1-yr OS of 55% with elraglusib/GnP and 35% with GnP to achieve 80% power with a chi-square test at a 2-sided 5% α. For OS, nonparametric log-rank test was used with statistical significance at p-value < 0.048. Cytokine/chemokine correlative biomarker assays were performed. The study completed enrollment in February 2024. **Results:** As of November 15, 2024 (preliminary data cut-off date), the primary analysis set included 155 pts in the elraglusib/GnP arm and 78 pts in the GnP arm, with 52.8% males and 57.5% ECOG PS 1. Median (range) CA 19-9 levels were 1568 U/mL (1 to 381,904 U/mL) in the elraglusib/GnP arm and 1590 U/mL (2 to 501,000 IU/mL) in the GnP arm. The 1-yr OS rate was 43.6% with elraglusib/GnP vs 22.5% with GnP (z-test p = 0.002); the mOS was 9.3 mo with elraglusib/GnP vs 7.2 mo with GnP (HR, 0.63; log rank p = 0.016; see Table). 38.1% of pts on elraglusib/GnP and 19.2% on GnP are censored, with the majority at $>$ 10 months OS. Several biomarkers appear to be predictive for OS including IFNβ and PD-L1. The most common TRAE with elraglusib/GnP was grade 1-2 transient visual impairment in $>$ 60% of patients (vs 9% with GnP). Grade ≥3 TEAEs occurred in 89.7% of pts on elraglusib/GnP and 80.8% on GnP. Most common grade ≥3 TEAEs with elraglusib/GnP (vs GnP) were neutropenia 51.6% (vs 29.5%), anemia 24.5% (vs 29.5%), and fatigue 16.1% (vs 5.1%). **Conclusions:** The preliminary results showed a statistically significant benefit for 1-yr OS and mOS and favorable trends for ORR and DCR with elraglusib/GnP over GnP, with manageable safety profile. The mOS for GnP is lower relative to MPACT and NAPOLI-3 but comparable to recent real-world meta-analyses, explained by advanced disease burden and higher mortality rate in the first 4 months in our study. Topline analysis (April 2025) and correlative biomarker analysis predictive for OS will be presented. Clinical trial information: NCT03678883. Research Sponsor: Actuate Therapeutics, Inc.

Preliminary efficacy results.

	Elraglusib/GnP n=155	GnP n=78
1-year OS, %	43.6	22.5
z-test p=0.002		
mOS, mo	9.3	7.2
HR=0.63; log-rank p=0.016		
Events, n (%)	96 (61.9)	63 (80.8)
mPFS, mo	5.6	4.9
HR=0.91; p=NS		
Events, n (%)	128 (82.6)	70 (89.7)
DCR, %	42.6	33.3
ORR, n (%)	43 (27.7)	16 (20.5)

A phase III randomized clinical trial evaluating perioperative therapy (neoadjuvant chemotherapy versus chemoradiotherapy) in locally advanced gallbladder cancers (POLCAGB).

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Background: Locally advanced Gallbladder cancers (LAGBC)initially deemed not suitable for R0 resection receive either neoadjuvant chemotherapy (NACT)or neoadjuvant chemoradiation (NACRT)downstaging for resection and to improve outcomes. **Methods:** This is a randomized phase 3 trial (NCT02867865) that included fit patients with LAGBC adenocarcinoma,. T3/T4 with liver infiltration ($>$ 2cm, $<$ 5cm); N1 nodal status; obstructive jaundice (type I/II biliary obstruction) ;duodenal or colonic abutment with no mucosal infiltration , $<$ 180°vascular involvement. The patients were randomized (1:1) to NACT arm (Gemcitabine + platinum for four cycles) versus NACRT arm (55 -57Gy with concurrent gemcitabine followed by two cycles of chemotherapy) and were then evaluated for surgery. A sample size of 314 patients was required to detect a 5.5 months difference (11 mo.to 16.5 mo in the test arm) with median overall survival (OS) as the primary endpoint (hazard ratio, 0.7; 2-sided α = 0.05; β = 0.2). Secondary endpoints were event free survival (EFS),R0 resection rates and post-operative complication rates. Due to slow accrual Institutional Ethics committee requested the investigators for interim analysis and approval was obtained for the same. **Results:** From Oct 2016 to Sept 2024, 124 patients (64 NACT, 60 NACTRT)were enrolled at 2 centers. At the time of analysis 93 OS events were observed in 124 patients. Median follow-up was 62 (range 6.9-94) months. More number of patients underwent R0 resection in NACRT than NACT arm 51.6 vs 29.7% (p = 0.01) In the intention to treat analysis, the NACTRT arm showed improved OS compared to the NACT arm [21.8 mo.vs.10.1 mo. p = 0.006]. EFS was 10.6 mo. vs 4.9 months, p = 0.006]. Similar results were noted in the per protocol analysis(n = 110). Clavien Dindo postoperative morbidity of grade 3 and above was 4/22 (18.18%) in NACT arm vs 9/32(28.12%) in NACRT arm (p = 0.30). The interim analysis demonstrated a significant improvement in efficacy in the NACRT arm. Based on the current data, the conditional power was calculated to be 99.96%. **Conclusions:** This trial demonstrates that the addition of concurrent chemoradiation to chemotherapy improves overall survival and resection rates in patients with locally advanced gallbladder cancers. These results provide important evidence to guide treatment decisions in this traditionally difficult to treat set of gallbladder cancers. Clinical trial information: NCT02867865. Research Sponsor: Intramural funding - Tata Memorial Centre.

Treatment outcomes.

Outcome measures	NACTRT N=60	NACT N=64	HR	p
Patients surgically explored	39(65%)	29(45.3%)		0.03
Patients undergoing R0 resection	31 (51.6%)	19 (29.7%)		0.01
Median OS (months) (95% CI)	21.8 (14.6-29.14)	10.1 (8.5-11.7)	HR- 0.56	0.006
5 Year survival (95% CI)	27 (17.7-43)%	18 (10-31) %	95%CI- 0.37-0.84	
EFS (months) (95% CI)	10.6 (6.07-15.5-15)	4.89 (3.06-6.73)	HR-0.58	0.006
5 Yr EFS (%)	21 (12-35.7)%	12.7 (6-24.6)%	95%CI- 0.39-0.85	

4008 Oral Abstract Session

Neoadjuvant chemotherapy with gemcitabine plus cisplatin followed by radical liver resection versus immediate radical liver resection alone followed adjuvant therapy in biliary tract cancer: Final results from the phase III AIO/CALGP/ACO-GAIN-Trial.

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Background: Radical surgical resection represents the only potentially curative treatment option for Biliary Tract Cancer (BTC) and (incidental) Gallbladder Carcinoma ((I)GBC). Nevertheless, 5-year OS is only 20–40% after curatively intended resection and data regarding pure adjuvant chemotherapy in BTCs are currently conflicting. Encouraging results of neoadjuvant/perioperative concepts in other malignancies provide a rationale to use this treatment in the early phase management of GBC and intrahepatic as well extrahepatic cholangiocarcinoma (ICC/ECC). **Methods:** GAIN is a multicenter, randomized, controlled, open-label phase III trial, including patients (pts) with localized or locally advanced resectable non metastatic biliary tract cancer (intra-/extrahepatic cholangiocarcinoma ICC/ECC; GBC in front of radical liver resection). Pts were randomized to either neoadjuvant (perioperative) systemic chemotherapy (Gemcitabine + Cisplatin 3 cycles pre- and post-surgery) followed by radical surgery (Arm A) or to direct surgery followed by adjuvant treatment (Arm B) according to investigators choice. Primary endpoint was OS; secondary endpoints were PFS/EFS, R0-resection rate, toxicity, perioperative morbidity, mortality and QoL. Recruitment was stopped after enrollment of 68 pts due to a slow enrollment rate. **Results:** Between Dec 2019 and Feb 2024, 68 pts were randomized and the ITT comprised 32 pts in Arm A and 30 pts in Arm B. Baseline characteristics were similar between arms (overall, male 55%; median age 66.0; cT3/T4 29.0%; cN+ 30.6%; 37.1% ICC, 30.6% ECC and 32.3% GBC). 90.6% of pts in Arm A completed all 3 pre-operative cycles. 43.8% in Arm A completed adjuvant treatment and 23.3% in Arm B received adjuvant treatment. Median follow-up was 11.8 months. Neoadjuvant treatment improved OS (mOS, Arm A 27.8 vs. 14.6 months Arm B; HR 0.46 [0.22 - 0.96]; p = 0.04) and R0 resection rate (62.5% vs 33.3%). This effect was also seen in event-free survival. Post-operative morbidity rates were similar in both arms (33.3% (A) vs. 32% (B)) and the 30- and 90-days mortality rates were lower for Arm A (30-days: 4.2% vs. 24%; 90-days: 4.2% vs. 28%). No new safety/toxicity signals were observed. In Arm A, 12 pts (38.7%) had at least one treatment related adverse event (TRAE) with grade 3 and 1 pt (3.2%) with grade 4. No fatal TRAEs were observed. **Conclusions:** Neoadjuvant / perioperative gem/cis clearly improved OS and R0 resection rate in pts with biliary tract cancer compared to direct surgery and was able to nearly double mOS while not increasing the morbidity rate and even decreasing mortality rates. Clinical trial information: NCT03673072. Research Sponsor: None.

Maintenance with OSE2101 plus FOLFIRI vs FOLFIRI alone after FOLFIRINOX (FFX) induction in patients (Pts) with advanced pancreatic ductal adenocarcinoma (aPDAC): Primary endpoint results of a randomized TEDOPAM GERCOR D17-01 PRODIGE 63 trial.

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Background: OSE2101 is an off the shelf vaccine made of 10 synthetic HLA-A2-restricted peptides targeting 5 tumor associated antigens. This multicenter, randomized, non-comparative, phase II study assessed FOLFIRI ± OSE2101 maintenance in aPDAC Pts without progression after 8 cycles of FFX. **Methods:** Eligible aPDAC Pts were randomized to FOLFIRI (Arm A) or FOLFIRI + OSE2101 (Arm B: subcutaneous injection on D1, D15, Q4W/6 doses then Q8W to M12 then Q12W up to M24). Stratification factors: tumor stage (locally advanced vs metastatic), best response to FFX (partial or complete response [CR, PR] vs stable disease [SD]), and center. Primary endpoint: overall survival (OS) rate at M12 in evaluable Pts (M12-OS; Fleming 2-stage design, H0: 25%; H1: 50%, 1-sided alpha: 2.5%, power: 90%); secondary endpoints: progression-free survival (PFS; RECIST v1.1), best response, duration of disease control (DDC), and safety. **Results:** 107 Pts (ITT) were randomized (53/Arm A, 54/Arm B) between 04/2021 and 05/2023. Median age 64 years (range:37-81), 53% men, 69% had metastases, 36%/64% had PR/SD to prior FFX. No evidence of imbalance in Pt characteristics was observed between arms. Median number of OSE2101 injections was 7.5 (1-14). Median treatment duration of FOLFIRI was 5.4 months in both arms. At data cut-off (Dec 9, 2024), median follow-up was 21.4 months with 101 evaluable Pts for M12-OS (49/Arm A, 52/Arm B; 4 consent withdrawals, 1 Pt's decision, 1 treatment interruption >4 weeks). Number of death events (n/%) was 19/35.8% in Arm A and 18/33.3% in Arm B. M12-OS (95%CI) was 61% (46.2%-74.8%) in Arm A and 65% (50.9%-78.0%) in Arm B. Median (95%CI) OS and PFS (ITT) were 17.3 months (10.6–23.2) and 8.2 months (5.3–11.6) in Arm A, and 15.5 months (12.4–19.3) and 7.8 months (5.4–10.6) in Arm B. Other secondary endpoints are described in Table. Among 33 Pts with SD to prior FFX in Arm B, 6 (18%) had CR/PR (1/5) when adding OSE2101 to FOLFIRI vs 5 (no CR) among 35 Pts in Arm A. In the safety population, 7 SAEs/6 Pts (12%) in Arm A and 22 SAEs/14 Pts (26%) in Arm B were reported. No unexpected SAEs were observed with OSE2101 except 1 inappropriate administration, and no evidence of increased toxicity of FOLFIRI with OSE2101. **Conclusions:** TEDOPAM met its primary objective with minimal toxicity and positive outcomes of adding OSE2101 cancer vaccine to maintenance FOLFIRI, albeit mitigated by unexpectedly favorable OS in the control arm. Two complete responses were observed when adding OSE2101. Further follow-up is ongoing and translational analysis planned. Clinical trial information: NCT03806309. Research Sponsor: OSE Immunotherapeutics.

ITT	Arm A N=53	Arm B N=54
Best response, n (%)		
CR	0 (0.0)	2 (3.7)
PR	12 (22.6)	10 (18.5)
SD	28 (52.8)	34 (63.0)
Progressive disease (PD)	8 (15.1)	8 (14.8)
Missing	5 (9.5)	0 (0.0)
DC rate, n (%)	40 (75.5)	46 (85.2)
DDC (95% CI)	8.8 (6.2-12.9)	9.8 (6.8-14.8)

Efficacy and safety of cafelkibart (LM-108), an anti-CCR8 monoclonal antibody, in combination with anti-PD-1 therapy in patients with pancreatic cancer: Results from phase 1/2 studies.

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Background: Targeting tumor-infiltrating Tregs presents a promising strategy to overcome resistance to immunotherapy in cancer treatment. LM-108 is a novel Fc-optimized anti-CCR8 monoclonal antibody designed to selectively deplete tumor-infiltrating Tregs while sparing peripheral Tregs. This pooled analysis of two phase 1/2 trials assesses the efficacy and safety of LM-108 in combination with anti-PD-1 therapy in patients with pancreatic cancer. **Methods:** Eligible patients (pts) with pancreatic cancer who had progressed on or after at least one prior line of systemic therapy were included. Treatment regimens included LM-108 at doses of 3 mg/kg Q3W, 3 mg/kg Q2W, 10 mg/kg Q3W, or 10 mg/kg Q2W, in combination with pembrolizumab (400 mg Q6W) or toripalimab (240 mg Q3W). The primary endpoint was ORR. Secondary endpoints were DCR, PFS, OS, DoR, safety, and biomarkers analysis. Data cutoff: December 2, 2024. **Results:** A total of 80 pts (median age: 63 years; 58.8% male) from China and Australia were treated. Of these, 48 pts had progressed on or after 1 prior line of therapy, and 32 pts had ≥2 lines. Eighteen pts (22.5%) had prior anti-PD-1 therapy, and 52 pts (65.0%) had liver metastases at baseline. TRAEs were reported in 76 pts (95.0%). Common TRAEs (≥25%) included increased AST, increased ALT, anemia, rash, pyrexia, decreased platelet count and increased conjugated bilirubin. Grade ≥3 TRAEs occurred in 42 pts (52.5%), the most common events (≥5%) were lipase elevation (7.5%), increased ALT (6.3%), increased AST (5.0%), immune-mediated enterocolitis (5.0%), hypokalemia (5.0%), and rash (5.0%). Median follow-up was 10.48 months (95% CI 7.20-12.65). Among 74 efficacy-evaluable pts, ORR was 20.3% (95% CI 11.8-31.2%) and DCR was 62.2% (95% CI 50.1-73.2%). Median DoR was 5.49 months (95% CI 3.02-8.87), PFS was 3.12 months (95% CI 1.61-4.86), and OS was 10.02 months (95% CI 6.41-13.11). Among 45 pts who had progressed on or after one prior line of therapy, ORR was 24.4% (95% CI 12.9-39.5%) and DCR was 71.1% (95% CI 55.7-83.6%), with a median DoR of 6.93 months (95% CI 3.02-NA), PFS of 4.86 months (95% CI 2.79-6.90), and OS not reached. The 12-month OS rate was 51.6% (95% CI 31.4-68.5%). Among these, 9 pts with high CCR8 expression (7 with baseline liver metastases) showed ORR of 33.3% (95% CI 7.5-70.1%) and DCR of 77.8% (95% CI 40.0-97.2%). Median PFS was 6.90 months (95% CI 1.22-NA), and OS was 9.15 months (95% CI 3.61-NA). **Conclusions:** LM-108 in combination with anti-PD-1 therapy demonstrated encouraging antitumor activity and a manageable safety profile in patients with pancreatic cancer who had progressed on or after prior systemic therapies. These findings support further investigation of LM-108 in combination with anti-PD-1 therapy as a potential treatment option for pancreatic cancer. Clinical trial information: NCT05199753; NCT05518045. Research Sponsor: LaNova Medicines Limited.

4011 Clinical Science Symposium

NeoPancONE: GATA6 expression as a predictor of benefit to peri-operative modified FOLFIRINOX in resectable pancreatic adenocarcinoma (r-PDAC): A multicentre phase II study.

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Background: Modified FOLFIRINOX (mFFX) is increasingly used in the perioperative setting in r-PDAC and patients (pts) would benefit from a biomarker approach. GATA6 expression enriches for the classical RNA subtype, associated with improved OS in advanced PDAC. Low expression identifies the basal subtype which may predict mFFX resistance. NeoPancONE is a single arm Phase II multicentre study evaluating clinical outcomes and investigating GATA6 as a biomarker of response to perioperative mFFX in r-PDAC. **Methods:** Pts were enrolled following central radiology review (CRR) and underwent an EUS FNB for GATA6 in-situ hybridization (ISH). Six cycles of mFFX were planned pre and postoperatively. The primary endpoint was 1 yr event-free survival (EFS) according to GATA6 ISH (high vs low). Secondary endpoints include OS, RECIST response, SAEs, R0 resection rates and RNA subtyping by PurIST. Statistical assumptions used a ratio of 3:1 GATA6 high:low, with a 1 yr EFS of 65% for high and 34% for low (HR 2.5, 80% power, 2 sided alpha 0.05). KM method and log-rank test were used. **Results:** Between Sep-2020– Sep 2023, 146 pts were screened and 84 enrolled (58%) at 8 Canadian centres. CRR deemed 39 (27%) ineligible. Clinical data are summarized (Table). GATA6 ISH was analysed in 74 (88%); 62 (84%) were high, 16% low. At a median follow up of 24.5 mos, the med EFS and OS in the ITT were 16.1 mos (95 CI; 13-21) and 34.2 mos (95 CI; 28-NE). Med OS in the 73 pts who underwent surgery was 35.6 mos (95 CI 33-NE). The 1 yr EFS was 71% in GATA6 high vs 58% in GATA6 low p= 0.53. 1 yr OS was 87% in high vs 75% for low p= 0.29. The proportion progressing within 6 mos of enrollment in the GATA6 low group was significantly higher (42% vs 12% p=0.02). PuriST subtyping was reported in 49 (67%) resections; 14% basal, 86% classical. The 1 yr EFS was 79% in classical vs 43% in the basal subtype p=0.1. The 1 yr OS was 95% in classical vs 57% in basal p=0.034. **Conclusions:** This is one of the first trials in r-PDAC to identify potential biomarkers to predict perioperative mFFX response. GATA6 by ISH can be assessed on baseline tissue. GATA6 high is a prognostic biomarker, although NS, trends towards improved EFS and an encouraging OS. Disease progression within 6 months of enrollment occurs in nearly 50% of patients with low GATA6 expression. Neo-adjuvant mFFX should not be the standard of care in these patients. Basal/Classical subtyping had stronger prognostic value than GATA6 and should be considered at baseline EUS FNB for future perioperative strategies in r-PDAC studies. Clinical trial information: NCT04472910. Research Sponsor: Princess Margaret Cancer Foundation UHN; Pancreatic Cancer Canada.

Characteristic n=84	
Age med. (range) yrs	64 (44, 83)
Baseline EUS FNB tissue n (%)	83 (98)
Pre-op completed 6 cycles n (%)	62 (74)
Pre-op RECIST CR/PR/SD/PD/NE %	1/18/64/11/6
Surgery Completed Y/N n (%) / R0 / R1 n (%)	73 (87) / 11(13) / 62 (85) / 11 (15)
Adjuvant Chemotherapy Y / N n (%)	63 (86) / 10 (14)
mFFX associated SAE ≥G3 n (%)	13 (15)
Pre-op mFFX related deaths	3 (4)

LBA4012 **Rapid Oral Abstract Session**

Disitamab vedotin (DV) plus toripalimab (Tor) and chemotherapy (C)/trastuzumab (Tra) as first-line (1L) treatment of patients (pts) with HER2-expressing locally advanced or metastatic (la/m) gastric cancer.

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Long-term outcomes and overall survival (OS) for zanidatamab + chemotherapy in HER2-positive (HER2+) advanced or metastatic gastroesophageal adenocarcinoma (mGEA): 4-year follow-up of a phase 2 trial.

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Background: Zanidatamab (zani), a dual HER2-targeted bispecific antibody, plus chemotherapy (chemo) has previously demonstrated antitumor activity and a manageable safety profile in the first-line (1L) treatment of patients (pts) with HER2+ mGEA. Here, we report a 4-year follow-up and the first report of both median OS and translational data from this phase 2 trial. **Methods:** The phase 2 trial (NCT03929666) evaluated zani + chemo (mFOLFOX6, CAPOX, or FP) in the 1L treatment of mGEA. In Part 1, pts had HER2-expressing (IHC 3+ or 2+) mGEA. Pts in Part 2 had HER2+ (IHC 3+ or IHC 2+/FISH+) mGEA by central assessment. After 25 pts were treated, antidiarrheal prophylaxis was added for cycle 1. The primary endpoint was confirmed objective response rate (cORR). Secondary endpoints included duration of response (DoR), progression-free survival (PFS), OS, and safety outcomes. Plasma ctDNA samples were collected for NGS testing (Guardant360). **Results:** In total, 46 pts were enrolled (zani + mFOLFOX6 [n = 24], CAPOX [n = 20], or FP [n = 2]). The majority (41 [89%]) of pts had HER2+ mGEA by central confirmation (ccHER2+); 35 (76%) pts had gastric/GEJ cancer. As of July 28, 2024, the median (range) follow-up was 48 (29-59) mo; 8 pts (17%) were on zani treatment and 19 (41%) in survival follow-up. Efficacy results are shown in the Table. The median OS was 36.5 mo; longest survival time was 57.9 mo (censored without death at data cutoff). The concordance between HER2 gene amplification by centrally assessed ISH vs plasma ctDNA was 90% (18/20). Of 14 pts with matched plasma samples at baseline and on-treatment (Cycle 2, day 15), 8 had a $>$ 90% decrease in total ctDNA levels and 2 had a decrease in HER2 copy number. Common ($>$ 5% of pts) grade 3 or 4 treatment-related AEs (TRAEs) were diarrhea (n = 18 [39%]), hypokalemia (n = 10 [22%]), vomiting (n = 4 [9%]), and nausea (n = 3 [7%]). Grade 3 or 4 diarrhea incidence was reduced from 52% to 24% after prophylaxis implementation. No deaths occurred due to TRAEs. **Conclusions:** After a median 4-year follow-up, zani + chemo demonstrated clinically meaningful efficacy in the 1L treatment of HER2+ mGEA, with durable responses and a median OS $>$ 3 years, and a manageable safety profile. Zani + chemo markedly reduced total plasma ctDNA levels early in treatment of mGEA. Clinical trial information: NCT03929666. Research Sponsor: Jazz Pharmaceuticals.

	All pts (N = 46)	ccHER2+ GEA pts (n = 41)
cORR[a], n (% [95% CI])	32 (76.2 [60.5, 87.9])	31 (83.8 [68.0, 93.8])
Median DoR[b] (95% CI), mo	18.7 (10.4, 44.1)	20.4 (8.3, 44.1)
24-mo DoR, % (95% CI)	40 (22, 58)	41 (22, 59)
Median PFS (95% CI), mo	12.5 (8.2, 21.8)	15.2 (9.5, 33.4)
Median OS (95% CI), mo	36.5 (23.6, NE)	36.5 (23.6, NE)
24-mo OS, % (95% CI)	65 (49, 77)	67 (49, 79)
36-mo OS, % (95% CI)	53 (37, 67)	53 (36, 67)
TRAEs, n (%)		
Any	46 (100)	41 (100)
Grade 3 or 4	30 (65)	26 (63)

[a]Response evaluable (n = 42 and 37).
[b]Complete or partial response. NE, non-estimable.

Recurrence patterns in the prospective, randomized, controlled, multicenter phase III ESOPEC trial comparing perioperative chemotherapy with preoperative chemoradiotherapy in patients with esophageal adenocarcinoma.

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Background: The ESOPEC trial (NCT02509286) showed that perioperative chemotherapy improved overall and progression free survival in pts with esophageal adenocarcinoma (EAC) compared with preoperative chemoradiotherapy. Understanding of the pattern of recurrence is important for the development of more effective future treatment strategies. **Methods:** Pts with cT1 cN+ cM0 or cT2-4a cNany cM0 EAC undergoing preoperative chemotherapy with FLOT (5-FU/leucovorin/oxaliplatin/docetaxel) or preoperative chemoradiotherapy with CROSS (41.4Gy/carboplatin/paclitaxel) plus tumor resection from the ESOPEC trial were eligible. Recurrence-free survival (RFS), distant metastasis-free survival (DMFS), and patterns of local, regional and distant recurrence were analyzed. Treatment groups were compared with respect to sites of recurrence by calculating 3-year cumulative incidences considering competing events, and by Cox regression models for event-specific hazards stratified by trial center and including treatment assignment (FLOT vs CROSS), cN stage (cN0 vs cN+), and age as covariates. Event-specific hazard ratios (HR) with two-sided 95% confidence intervals (CI) and p-values are presented. **Results:** Of the 438 pts enrolled in ESOPEC, 192 of 221 (86.9%) in the FLOT group and 179 of 217 (82.5%) in the CROSS group underwent tumor resection and represent the population for this analysis. R0 resection was achieved in 354 pts (182 (94.8%) FLOT; 172 (96.1%) CROSS). 142 (74.0%) pts in FLOT received postoperative chemotherapy. After a median follow-up of 56 months 178 pts had disease recurrence (81 FLOT; 97 CROSS), and 28 pts died without recurrence (12 FLOT; 16 CROSS). The 3-year RFS rate was 54.5% in FLOT vs 39.0% in CROSS (HR for recurrence or death 0.67; 95% CI, 0.51 - 0.89, p = 0.005). The 3-year DMFS rate was 57.6% in FLOT vs 41.0% in CROSS (HR for distant recurrence or death 0.64; 95% CI, 0.48 – 0.85, p = 0.002). **Conclusions:** Perioperative chemotherapy with FLOT improves RFS and DMFS compared to preoperative chemoradiotherapy with CROSS in EAC. The prognosis of pts is determined by distant recurrence, which is less common after FLOT than CROSS. Clinical trial information: NCT02509286. Research Sponsor: German Research Foundation (DFG); 264590883.

Treatment group comparisons regarding site of recurrence.

	FLOT N=192	CROSS N=179	FLOT vs CROSS		
Site of recurrence	N (%)*	N (%)*	HR (for recurrence)	95% CI	P-value
Locoregional	39 (20.2)	32 (17.4)	1.00	0.62 – 1.61	0.99
Local	19 (9.5)	15 (8.1)	1.03	0.51 – 2.06	0.94
Regional	29 (15.1)	27 (14.5)	0.89	0.52 – 1.52	0.68
Distant	64 (31.5)	89 (47.2)	0.59	0.43 – 0.82	0.002
Distant lymphatic	21 (9.3)	31 (15.6)	0.60	0.34 – 1.05	0.074
Hematogenous	33 (17.2)	48 (26.1)	0.59	0.37 – 0.92	0.021
Pleural/Peritoneal	24 (12.0)	31 (16.4)	0.63	0.36 – 1.09	0.10

*% calculated as 3-year cumulative incidence.

4015 Rapid Oral Abstract Session

Decoding the response and resistant features to the Claudin18.2-specific CAR-T cell CT041 in gastric cancer: A multi-omics exploratory biomarker analysis of the phase 1 clinical trial.

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Background: CT041, a Claudin18.2-specific CAR-T cell therapy against gastric cancer (GC), has demonstrated encouraging efficacy and a manageable safety performance. However, the characteristics of response and resistance to CT041 therapy remain unclear. **Methods:** An exploratory biomarker analysis of the phase 1 CT041-CG4006 clinical trial (NCT03874897) was conducted. Baseline samples were collected from primary tumors (PT), and dynamic samples were collected from peripheral blood and malignant ascites at day 0, 3, and 7 of 35 patients. These samples underwent single-cell RNA sequencing (n = 41), spatial transcriptomics (ST, n = 8 for Visium V2 and n = 5 for Xenium 5K), and multiplex immunofluorescence detection (n = 28). **Results:** In the responders, significantly higher GZMK+CD8+ T-lymphocyte infiltrates, which were in a progenitor-like exhausted (Tpex) state, were identified within PT. More GZMK+ Tpex infiltration also correlated with better prognosis (high vs. low: progression-free survival 9.98 vs. 5.45 months, P = 0.020; overall survival 18.03 vs. 8.03 months, P = 0.038), manifesting superior potential as a predictor of CT041 response (AUC 0.87, 95%CI 0.72-1.00). Moreover, strong and positive associations between GZMK+ Tpex and IRF8+ B-lymphocytes were discovered. ST detection further uncovered that they tended to co-localize within tertiary lymphoid structures and intimately interacted via the MHC-I and CCL5-CXCR4 pathways. In cases resistant to CT041, significantly higher infiltrates of IQGAP3+ cancer cells, a subset characterized by augmented proliferative activity, were discovered. While IQGAP3+ cancer cells hindered the infiltration of GZMK+ Tpex, they exhibited a co-infiltrated pattern with IL6+ fibroblasts, wherein enhanced epithelial-to-mesenchymal transition pathway activity was noted. Through dynamically parsing the blood and ascites samples, an initial activated and subsequent exhausted state of GZMK+ cytotoxic T-lymphocyte was observed after the infusion of CT041. Additionally, significant up-regulation of NR4A1, a crucial regulator of Tpex, and CCR9, a key homing molecule to the gastrointestinal mucosa, of peripheral T-lymphocytes was detected in responsive cases. **Conclusions:** This exploratory analysis first unveiled the biological underpinnings and clinical implications of GZMK+ Tpex in determining response and resistance to the Claudin18.2-specific CAR-T therapy. Research Sponsor: Integrated Project of Major Research Plans of the National Natural Science Foundation of China; Joint Fund for Regional Innovation and Development of the National Natural Science Foundation of China.

Cosiporfin sodium (DVDMS)-mediated photodynamic therapy (PDT) versus treatment of physician's choice (TPC) in patients (pts) with advanced esophageal cancer (aEC): A phase III, randomized, open-label, multicenter trial.

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Background: Challenges persist in the treatment of aEC, particularly for pts with esophageal stenosis and dysphagia, conditions that deteriorate the nutrition status and hinder anti-tumor therapies, leading to dismal prognosis. Building on the promising anti-tumor activity and improvement in dysphagia in a phase II single-arm trial, the phase III DYNA-Esophagus03 trial assessed DVDMS, a novel photosensitizer, -mediated PDT in aEC, comparing to TPC. **Methods:** Pts with local recurrence or metastasis EC and Stoller dysphagia grade ≥2, stratified by previous treatment lines (1^{st} vs 2^{nd}-line), were randomized 2:1 to DVDMS-mediated PDT (PDT delivered 24 hours after 0.2 mg/kg DVDMS injection at a light dose of 102 J/cm² and wavelength of 630±5 nm) or TPC. The primary endpoint was esophageal stenosis overall response rate (es-ORR) assessed by endoscopy at 28 days. A sample size of 186 pts achieved a 90% power to detect an es-ORR increase from 10% to 35% at a 1-side 2.5% level, considering a 30% drop-off rate. **Results:** As of November 11, 2024, 186 pts were randomly assigned (124 DVDMS-PDT group/62 TPC group). The baseline characteristics were: mean age 67.6 ± 8.7 years, 32.3% distant metastasis, 52.2% grade 3 dysphagia, and 1.1% grade 4. The es-ORR was 51.6% with DVDMS-PDT vs 8.1% with TPC at day 28 ($P < 0.0001$). At a median follow-up of 8.9 months (mos), the median progression-free survival was 2.8 vs 2.2 mos (HR = 0.61, 95%CI 0.40-0.93; P = 0.0244), respectively. Time to progression was 5.9 vs 3.9 mos (HR = 0.45, 95% CI: 0.25-0.82, P = 0.0056). Median overall survival (OS) was 7.0 vs 6.4 mos (HR = 0.88, 95%CI 0.59-1.32; P = 0.5169), respectively. Considering the high cross-over rate (45.2%), the rank preserving structural failure time-adjusted median OS was 7.0 vs 4.7 mos (HR = 0.64, 95%CI 0.42-0.97; P = 0.0223). The improvement of dysphagia and quality of life are detailed in the Table. Phototoxicity was negative in 64.9% pts in DVDMS-PDT group on day 7, increasing to 91.4% by day 28. Grade ≥3 treatment-emergent adverse events occurred in 38.2% of the DVDMS-PDT group and 49.2% of the TPC group. Six deaths were due to treatment-related adverse events (4.9%) were reported in the DVDMS-PDT group and 5 (8.5%) in the TPC group. **Conclusions:** DVDMS-PDT significantly improved esophageal stenosis and dysphagia compared to the treatment of physician's choice in pts with aEC, with prolonged PFS and TTP, potential better OS and a manageable safety profile. Clinical trial information: CTR20221271. Research Sponsor: None.

	DVDMS-PDT (n=124)	TPC (n=62)
Reduction at least 1 grade in Stooler's score in 6 mons, %	47.8%	8.6% (P<0.0001)
Change in EORTC QLQ-C30 total score	-26.7 ± 2.5	-39.8 ± 4.3
Change in dysphagia score	16.0 ± 2.6	24.6 ± 4.3
Change in eating score	16.9 ± 2.4	30.6 ± 4.1

Values are least-squares mean ± standard error unless otherwise noted.
Symptom scores were assessed using EORTC QLQ-OES18.

Claudin18.2 (CLDN18.2) expression and efficacy in pancreatic ductal adenocarcinoma (PDAC): Results from a phase I dose expansion cohort evaluating IBI343.

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Background: CLDN18.2 is highly expressed in nearly 60% of PDAC cases. Yet to date, there are no approved targeted therapies and prognoses for these patients (pts) remain poor. IBI343, consisting of an anti-CLDN18.2 Fc silenced monoclonal antibody and the topoisomerase I inhibitor, exatecan, is the first CLDN18.2 antibody-drug conjugate to have shown encouraging efficacy in PDAC. Here, we report results from a phase 1 study (NCT05458219) in pts with PDAC treated with IBI343 by CLDN18.2 expression status (≥60% vs < 60%). **Methods:** Eligible pts with advanced PDAC and moderate to high expression of CLDN18.2 (defined as immunohistochemistry [IHC] membrane staining intensity ≥2 in ≥40% of tumor cells by IHC VENTANA CLDN18 [43-14A] Assay) who failed or were intolerant to standard treatment were enrolled. IBI343 was administered every 3 weeks at multiple dose levels (1, 3, 4.5, 6, 8, and 10 mg/kg). Endpoints included safety, objective response rate (ORR), disease control rate (DCR), duration of response (DoR), progression-free survival (PFS) per RECIST v1.1, and overall survival (OS). **Results:** As of December 27, 2024, 83 pts from China and Australia were enrolled. 44 and 12 pts with CLDN18.2 expression ≥1 in ≥60% (+) and < 60% (-) of tumor cells, respectively, received IBI343 at 6mg/kg in the dose expansion phase (median age, 60 and 64 years; male, 54.5% and 66.7%; received prior treatments ≥2L, 61.4% and 83.3%). Among all treated pts (n = 83), treatment-emergent adverse events (TEAEs) occurred in 82 (98.8%) pts and ≥Grade 3 (G3) TEAEs in 42 (50.6%) pts. TEAEs led to treatment discontinuation in 6 (7.2%) pts. No TEAE led to death. Most common TEAEs were anemia (66.3%, 15.7% ≥G3), neutrophil count decreased (48.2%, 9.6% ≥G3), and WBC count decreased (47.0%, 9.6% ≥G3). The safety profile of IBI343 in PDAC was comparable to previous reports. Among CLDN18.2+ pts (n = 44), confirmed ORR was 22.7% (95% CI, 11.5–37.8); DCR was 81.8% (95% CI: 67.3–91.8), median PFS was 5.4 (95% CI, 4.1–7.4) months (mos), median OS was 8.5 (95% CI, 6.6–12.1) mos, and in 10 pts with confirmed partial response median DOR was 6.7 (95% CI, 3.2–7.7) mos. Among CLDN18.2+ pts who received 1 and 2 lines of prior treatment, median OS was 12.1 (95% CI, 6.6–not calculable [NC]) mos and 9.1 (95% CI, 5.1–NC) mos, respectively. Among CLDN18.2- pts (n = 12), no pt had an objective response, DCR was 41.7% (95% CI: 15.2–72.3), median PFS was 1.4 (1.3–3.2) mos, which was shorter than what was seen in CLDN18.2+ pts (Ad hoc analysis: nominal P < .0001; HR = 0.198 [95% CI: 0.089-0.439]) and median OS was 6.2 (95% CI,1.4–9.0) mos. **Conclusions:** IBI343 was well tolerated and continues to show encouraging efficacy in pts with PDAC. Efficacy benefit was most pronounced in those with CLDN18.2 expression ≥60%, suggesting that CLDN18.2 can be a predictive biomarker for response to IBI343 in PDAC. The trial is enrolling in Australia, China, and US. Clinical trial information: NCT05458219. Research Sponsor: None.

Clinical activity of EBC-129, a first-in class, anti N256-glycosylated CEACAM5 and CEACAM6 antibody-drug conjugate (ADC), in patients with pancreatic ductal adenocarcinoma (PDAC) in a phase 1 study.

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Background: Pancreatic ductal adenocarcinoma (PDAC) is an aggressive malignancy with limited treatment options. EBC-129 is a first in class MMAE-linked ADC against N256-glycosylated CEACAM5/6 antigen. Pre-screening data shows 73% of PDAC express surface antigen (IHC positive cut-off ≥20% at 2+ or 3+) or 82% (≥1% at 3+). Previously reported dose escalation data identified 1.8 and 2.2 mg/kg every 3 weeks as the RP2Ds. Here we report pooled safety and efficacy data of the PDAC patients enrolled in the dose escalation (DEs) and expansion (DEx) cohorts of the phase 1 study. **Methods:** This study consisted of DEs and DEx cohorts. Previously treated histologically confirmed, locally advanced or metastatic PDAC patients with antigen expression levels of ≥20% at 2+ or 3+ intensity or ≥1% at 3+ intensity (IHC on archival samples) were enrolled. Objectives were to evaluate safety, efficacy, and PK of EBC-129, administered every 3 weeks. **Results:** A total of 21 PDAC patients were enrolled (6 in DEs and 15 in DEx). Patients received 1.8 (n = 8), 2.0 (n = 2) or 2.2 (n = 11) mg/kg EBC-129 every 3 weeks. 52% were male; mean age 63 years; median 3 (range 1-7) lines of previous treatments with 81% prior taxane treated. At data cut-off (Jan 16th, 2025), 5 patients are continuing treatment, 12 patients had radiological progression, 3 had clinical progression, and 1 patient withdrew treatment. The overall response rate, disease control rate (first assessment), and median PFS, at 1.8 mg/kg, 2.2 mg/kg and overall group, respectively, were 25.0%, 18.2% and 19.0% (unconfirmed), 87.5%, 63.6% and 71.4%, and 18, 12 and 12 weeks. 43% of patients had any tumour shrinkage overall. Infusion related reactions (IRR) were seen in 57% of patients; most were grade 1/2, more frequent at 2.2 mg/kg, and resolved or reduced with premedication. Grade ≥3 treatment related adverse events included neutropenia (50.0% and 81.8%) and anaemia (12.5% and 18.2%) at 1.8 and 2.2mg/kg, respectively; amylase/lipase increase, vomiting, and aspartate aminotransferase increase occurred in 1 patient each. Grade ≤2 peripheral neuropathy was seen in 2 patients. No drug related discontinuations occurred in this cohort. In this cohort, selected for target antigen expression, no apparent correlation was seen between IHC score and treatment response. Based on a cut-off of > 25% CEA decrease (either local or central), biomarker response was seen 42.9% at 1.8 mg/kg and 36.4% at 2.2 mg/kg. **Conclusions:** EBC-129 shows promising clinical activity in heavily treated PDAC patients with a manageable tolerability profile, consistent with MMAE-based ADCs. Further evaluation of EBC-129 in PDAC, both as monotherapy and in combination with chemotherapy, is planned. Clinical trial information: NCT05701527. Research Sponsor: Experimental Drug Development Centre (EDDC).

4019 Rapid Oral Abstract Session

10-year follow up of a phase 2 clinical trial of pembrolizumab (pembro) in microsatellite instability-high (MSI-H)/mismatch repair deficient (dMMR) advanced solid tumors.

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Background: Inhibitors of Programmed Cell Death Protein-1 (PD-1) have demonstrated remarkable activity in dMMR/MSI-H cancers, leading to the first tissue agnostic FDA approval for an oncologic indication. We report herein results of long-term follow up of KEYNOTE-016, the first study to demonstrate pan-tumor activity of the PD-1 inhibitor pembro in dMMR/MSI-H solid tumors. **Methods:** KEYNOTE-016 was a multi-center open-label phase 2 study evaluating pembro in patients with advanced colorectal cancer (CRC) (Cohort A) or non-CRC solid tumors (Cohort C) that were dMMR and had progressed after ≥1 prior line of therapy (or ≥2 prior lines for CRC). Eligible patients were age ≥ 18, and had measurable disease per RECIST 1.1. Patients with active CNS metastases, who were on immunosuppressive therapy, had autoimmune disease, or were previously treated with immune checkpoint inhibitors were excluded. Patients received pembro IV every 2 weeks until progression, intolerance, withdrawal of consent or up to a maximum of 2 years. **Results:** Between 9/2013 - 9/2017, 88 patients (Cohort A: 41; Cohort C: 47) enrolled at 7 sites and received ≥1 dose of pembro. Tumor types enrolled on Cohort C included endometrial (N = 15), pancreatic (N = 9), small intestinal (N = 5), gastroesophageal (N = 5), biliary (N = 4), ampullary (N = 4), and other (N = 5). Median follow up time was 49.7 mos for all patients and 99.8 mos for alive patients. Objective response rate (ORR) was 58% with 23 partial (PR) and 28 complete responses (CR). 16 patients experienced a best response of stable disease (SD) for a disease control rate of 76%. Median PFS and OS were 34.9 mos (95% CI: 14.8-NR) and 80.8 mos (95% CI: 33.2-NR) respectively. The 3-, 5-, and 10-year OS rates were 55.1%, 53.7% and 47.4% respectively. Outcomes were similar between Cohorts A and C (see Table). **Conclusions:** In summary, long term follow up of KEYNOTE-016 confirms high rates of durable remission from pembro in patients with dMMR/MSI-H solid tumors, with several patients remaining alive and in remission at 10+ years follow up. Responses were seen across tumor types. Clinical trial information: NCT01876511. Research Sponsor: Swim Across America; Merck.

Results by cohort.

	Cohort A CRC N=41	Cohort C non-CRC N=47
ORR, %	56.1	59.6
PR, N (%)	11 (27)	12 (25)
CR, N (%)	12* (29)	16 (34)
SD, N (%)	10 (24)	6 (13)
PD, N (%)	5 (12)	9 (19)
NE, N (%)	3 (7)	4 (9)
PFS, median months (95% CI)	38.8 (8.1-NR)	20.5 (14.3-NR)
OS, median months (95% CI)	80.8 (33.2-NR)	86.4 (21.8-NR)
Follow up time, median months	51.2	35.9
3-year OS rate (%)	60.5	50.3
5-year OS rate (%)	57.5	50.3
10-year OS rate (%)	47.3	47.2

*Includes 3 patients with unconfirmed CR.

Health-related quality of life (HRQOL) in the phase 3 trial of cabozantinib vs placebo for advanced neuroendocrine tumors (NET) after progression on prior therapy (CABINET, Alliance A021602).

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Background: In previously treated patients (pts) with advanced extra-pancreatic NET (epNET) or pancreatic NET (pNET), cabozantinib (cabo) demonstrated improved progression-free survival compared to placebo (pbo) in the CABINET trial (NCT03375320). Here we present HRQOL data from CABINET. **Methods:** Pts with previously treated unresectable, locally advanced or metastatic epNET or pNET were randomized (2:1) in separate cohorts to receive cabo 60 mg daily vs pbo. HRQOL was an exploratory endpoint measured using the EORTC QLQ-C30, QLQ-GI.NET21, Patient Global Impression of Change (PGIC), and PRO-CTCAE questionnaires. Optional participation was by paper surveys at baseline and every 12 weeks (wks) until disease progression or new anticancer therapy. Mean changes from baseline were compared between treatment arms at wk12 using general linear mixed models. Minimally important within-arm improvements and between-arm differences were defined as 8 points on the C30 Global Health Status (GHS)/QOL Scale. PGIC was dichotomized as improved vs unchanged/worsened and compared using Chi-squared tests. Rates of pt-reported adverse events (AEs) by PRO-CTCAE were baseline-adjusted and compared using Fisher's exact tests. **Results:** 172 pts (113 cabo, 59 pbo) with epNET and 81 pts (53 cabo, 28 pbo) with pNET consented for survey participation. Pts completed 524 (82%) of 640 expected surveys across baseline, wk12, and wk24. For epNET, C30 GHS/QOL was significantly improved at wk12 in pts receiving cabo (mean change 9.5, standard error (SE) 2.2, $p < 0.001$) but not pbo (mean change 0.2, SE 3.1, $p = 0.95$) resulting in significantly different mean changes from baseline between arms ($p = 0.02$). For pNET, C30 QHS/QOL was significantly improved at wk12 in pts receiving cabo (mean change 8.0, SE 3.0, $p = 0.008$) but not pbo (mean change 6.8, SE 4.4, $p = 0.12$); mean changes from baseline did not statistically differ between arms ($p = 0.82$). No significant differences in mean changes from baseline at wk12 in C30 Physical, Role, Emotional, Cognitive and Social Function were observed between arms in the epNET or pNET cohorts. In both cohorts at wk12, pts on cabo reported improved overall status as measured by PGIC more often than those on pbo (epNET: 38% vs 19%, $p = 0.04$; pNET: 57% vs 18%, $p = 0.006$). Rates of pt-reported AEs were statistically significantly higher in cabo for diarrhea (68% vs 53%), hand-foot syndrome (57% vs 26%), mouth or throat sores (47% vs 27%), and dysgeusia (67% vs 37%) [all $p < 0.05$]. GI.NET21 data will be presented. **Conclusions:** Although cabo is associated with pt-reported AEs consistent with its known safety profile, global HRQOL was maintained. A higher proportion of patients receiving cabo reported improved overall status. Results support cabo as a treatment option for pts with previously treated advanced NET that preserves patient HRQOL. Clinical trial information: NCT03375320. Research Sponsor: UG1CA189823; U10CA180821; U10CA180882; Exelixis; https://acknowledgments.alliancefound.org.

Claudin-18.2 expression in gastro-oesophageal adenocarcinoma in a Western population: Overlap with other biomarkers and prognostic value.

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Background: Claudin 18.2 (CLDN18.2) is a novel biomarker for response to anti-CLDN18.2 therapy in gastroesophageal adenocarcinoma (GEA). Based on prevalence data, originating mostly from an Asian population, 40% of GEA are CLDN18.2 positive. We currently lack information on the cross-prevalence of CLDN18.2, HER2-status, microsatellite instability (MSI) and PDL1 expression in a Western population of localized and metastatic GEA. **Methods:** We present a single-center, retrospective study including localized and metastatic GEA patients diagnosed between 2019-2023. Histopathology with MMR status, HER2 status (IHC/SISH) and PDL1 CPS was obtained. CLDN18.2-positivity defined as ≥75% of tumor cells showing moderate-to-strong membranous staining was determined by IHC using the VENTANA CLDN18 [43-14A] RxDx Assay and underwent blind review by independent expert pathologists. Baseline characteristics and clinical follow-up data were gathered until august 2024. Kaplan-Meier curves were constructed for overall survival (OS), progression/relapse free survival (PFS/RFS) and survival after recurrence (SAR). Unrestricted grants/support was provided from Astellas, AMGEN and Roche diagnostics. **Results:** Of 405 patients with GEA, 261 presented with localized and 144 with metastatic disease. The majority were male (71%) with a median age of 65 years. 59% of tumors were junction tumors and 41% were gastric cancers. dMMR was detected in 6%. HER2 positivity (cfr. TOGA criteria) was seen in 16% of cases. PDL1 CPS ≥1 prevalence was 58%. CLDN18.2 positivity was seen in 42% of patients. Double CLDN18.2-HER2 and CLDN18.2-dMMR positivity was rare (5% and 3%), but strikingly in absolute numbers, about one third of HER2 positive tumors and half of dMMR tumors were CLDN18.2 positive. Double CLDN18.2-PDL1 ≥1//≥5//≥10 positivity was seen in 23%,15% and 9%. In patients with localized disease CLDN18.2 positivity did not affect RFS (HR: 0.99; 95% CI(0.68-1.43); p = 0.95) and OS (HR: 0,78; 95%CI(0.52-1.16) p = 0,22) with a median follow-up (FU) of 42 months. In the remaining 113 patients with primary metastatic disease no difference in terms of PFS (HR: 1.17; 95%CI(0,79-1.73); p = 0,43) or OS (HR: 1.43; 95%CI(0,94-2.16); p = 0,1) was seen according to CLDN18.2 status with a median FU of 39 months. Median SAR in the localized group was statistically longer in the PDL1 CPS≥1 subgroup(HR: 0.51; 95%CI(0,34-0,79); p = 0,002). SAR was not different in CLDN18.2+ and CLDN18.2- patients (HR: 1,07; 95% CI(0,69-1.65) p = 0,77). **Conclusions:** We confirmed a 42% positivity rate of CLDN18.2 in a combination of localized and metastatic GEA in a Western population. dMMR was present in 6% of cases, PDL1 CPS ≥1 and HER2+ was seen in 58% and 16% of patients. CLDN18.2 positivity was strikingly present in half dMMR and one third of HER2+ cases. CLDN18.2 positivity did not affect survival in localized and metastatic disease. Research Sponsor: Astellas; Amgen.

Preliminary results of a phase 1 study of LB1908, an autologous Claudin 18.2–targeted chimeric antigen receptor T-cell product, in patients with advanced gastroesophageal adenocarcinoma.

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Background: Claudin 18.2 (CLDN18.2) is a potential therapeutic target expressed on most gastric, gastroesophageal, and esophageal adenocarcinomas (GC/GEJC/EC), with normal tissue expression limited to gastric epithelium. We present preliminary results of the dose-escalation trial of LB1908, a CLDN18.2-targeted autologous CAR-T cell product, in adults with advanced GC/GEJC/EC. **Methods:** This trial is an ongoing, open-label, multicenter, first-in-human phase 1 study of LB1908 in patients with advanced GC/GEJC/EC relapsed/refractory to ≥1 prior line of therapy (LOT), and with ≥1+ CLDN18.2 expression in ≥50% of tumor cells by central testing (43-14A antibody). A modified 3+3 design is used for dose escalation with planned dose levels of 0.5, 1.5, and 3×10^6 CAR+ T cells/kg. The primary objective is evaluation of safety and dose-limiting toxicities (DLTs) with secondary objectives of antitumor activity and pharmacokinetics. **Results:** As of the data cutoff of January 4, 2025, 6 patients were dosed with LB1908 at dose level 1 (0.5×10^6 cells/kg). Four patients had EC and 2 had GC, all with metastatic disease. Patients had a median of 2 prior LOTs; all had received fluoropyrimidine/platinum agents. Bridging therapy was administered to all patients between apheresis and LB1908 infusion, and patients received standard lymphodepletion (LD) with cyclophosphamide/fludarabine. All patients experienced treatment-emergent adverse events (TEAEs); the most common grade ≥3 TEAEs were hematologic and attributable to the LD regimen. Of grade ≥3 TEAEs related to LB1908, only gastritis/gastric mucosal injury occurred in more than 1 patient (n = 3), including 1 DLT. After implementation of toxicity management guidelines using prophylactic enteral beclomethasone and early systemic steroids, no patients experienced prolonged grade ≥3 upper GI AEs. CRS occurred in all patients, with no grade ≥3 events. No ICANS was observed. CAR-T cell expansion was seen in all patients, with a median C_{max} of 1594 copies/μg genomic DNA (range, 264-6922) and T_{max} of 14 days (range, 11-15). All 6 patients were evaluable for response, with 5 (83%) experiencing target lesion shrinkage (maximal 1%, 9%, 25%, 31%, and 41% reduction from baseline). Responses deepened over time in the 2 patients with multiple postinfusion scans (-25% and -41%, respectively), including 1 patient achieving a RECIST partial response 7 months after treatment. **Conclusions:** LB1908 demonstrates peripheral expansion and encouraging antitumor activity at the lowest dose tested, with a manageable safety profile. Implementation of a toxicity mitigation strategy ameliorated on-target gastric mucosal injury without compromising expansion kinetics or antitumor activity. Longer follow-up and data from patients treated with higher cell doses will be presented at the meeting. Clinical trial information: NCT05539430. Research Sponsor: Legend Biotech USA Inc.

Genomic landscape and biomarker analyses utilizing circulating-tumor DNA in advanced esophageal squamous cell carcinoma: Sub-analysis of SCRUM-MONSTAR GOZILA.

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Background: Advanced esophageal squamous cell carcinoma (ESCC) is a cancer type with a poor prognosis, with limited survival benefits from current multimodal approaches. The incomplete understanding of molecular mechanisms in advanced ESCC has hindered the development of effective targeted therapies, emphasizing the critical need for identifying predictive biomarkers and novel therapeutic targets. **Methods:** SCRUM-MONSTAR GOZILA is a nationwide plasma-based genomic profiling study utilizing Guardant360 in Japan, which aimed to analyze circulating tumor DNA (ctDNA) genomic alterations in patients with advanced solid tumors, including ESCC. We evaluated the genomic landscape with advanced ESCC patients and investigated associations between genomic alterations and overall survival (OS) using the log-rank test. The correlation between progression-free survival (PFS) and blood tumor mutation burden (bTMB) in immune checkpoint inhibitor (ICI) monotherapy was also assessed using multiple cut-off values (2, 4, 6, 8, and 10 mutation/Mb). **Results:** The present study included 313 patients with available genomic and clinical data. The gene alteration spectrum comprised mutations (single nucleotide variants, 71.6%; and insertions/deletions, 10.7%), copy number alterations (CNAs, 17.3%), and fusions (0.48%). TP53 was the most frequently altered gene (88.5%), followed by PIK3CA (36.4%), NFE2L2 (24.3%), CCND1 (22.4%), EGFR (20.1%), ATM (16.3%), FGFR1 (10.2%), BRCA2 (10.2%), MET (9.6%) and ARID1A (9.6%). Regarding the survival outcomes, PIK3CA CNA was significantly associated with worse OS compared to those with PIK3CA wild type [hazard ratio (HR), 1.84; 95% confidence interval (CI), 1.24–2.74; p-value, 0.0002], and PIK3CA mutation showed a trend toward shorter OS (HR, 1.43; 95%CI, 0.94–2.17; p-value, 0.06). Patients with both PIK3CA mutation and CNA exhibited significantly worse OS compared to those with PIK3CA wild type (HR, 1.94; 95%CI, 0.85–4.45; p-value, 0.03). Both FGFR1 CNA and mutation were associated with poorer OS (HR, 1.98; 95%CI, 1.03–3.79; p-value, 0.005; and HR, 2.84; 95%CI, 0.89–9.07; p-value, 0.002, respectively). CNA in CCND1 and EGFR, and mutation in NFE2L2 and RB1 also significantly correlated with worse OS (any p-value$\leq$0.01). Among 142 patients treated with ICI monotherapy, no statistically significant differences in PFS were observed at any cut-off value of bTMB (any p-value $>$ 0.1). **Conclusions:** This comprehensive analysis of ctDNA profiles revealed distinct genomic alterations with prognostic significance in advanced ESCC. Multiple alterations demonstrated significant associations with poor OS, meanwhile bTMB was not validated as an effective predictive biomarker for ICI efficacy. These findings provide insights into potential therapeutic targets and prognostic biomarkers in advanced ESCC. Clinical trial information: 2021-GB-009. Research Sponsor: None.

HER2 expression dynamics and prognostic significance in the treatment of gastric cancer.

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Background: The human epidermal growth factor receptor 2 (HER2) expression undergoes changes during the treatment of gastric cancer. This study aims to evaluate post-treatment HER2 expression changes and the impact on survival. **Methods:** From a prospectively maintained database, we extracted clinical and pathological data, treatment information, and survival outcomes of gastric cancer patients (pts) with paired pre- and post-treatment HER2 immunohistochemistry (IHC) results (2018-2024). Cohen's Kappa was used to assess HER2 expression concordance. Logistic regression was performed to identify factors associated with HER2 change, while the Kaplan-Meier method and Cox regression were used for survival analysis. **Results:** 274 gastric cancer pts with paired HER2 IHC results were enrolled, including IHC 0 (67.5%, 185/274), 1+ (14.6%, 40/274), 2+ (13.5%, 37/274), 3+ (4.4%, 12/274) before treatment and IHC 0 (63.8%, 175/274), 1+ (21.9%, 60/274), 2+ (11.7%, 32/274), and 3+ (2.6%, 7/274) after treatment. The overall HER2 change rate was 42.7% (21.5% HER2 expression increased, 21.2% decreased), indicating low concordance (Kappa = 0.179, $p < 0.001$). Among 7.6% (17/225) of pts with HER2 changes from 0/1+ to 2+/3+, 23.5% (4/17) received anti-HER2 therapy (trastuzumab or anti-HER2 ADCs), achieving a 75.0% response rate. 38.5% (5/13) of initially confirmed HER2-positive pts (IHC 3+/2+ and FISH+) exhibited loss of HER2 positivity after treatment. 3 of 8 initially HER2-negative pts who converted to HER2-positive received trastuzumab for metastatic diseases, achieving a 66.7% response rate. Based on efficacy evaluation on the second HER2 testing, 197 pts were classified into the PR/SD group and 77 into the PD group, with comparable HER2 changes rate (41.6% vs. 45.5%, p = 0.565). Anti-HER2 therapy (n = 28) was associated with a higher HER2 changes rate (67.9% vs. 39.8%, p = 0.005), mainly driven by HER2 reduction (60.7% vs. 16.7%, $p < 0.001$). Multivariate logistic regression showed that combined immunotherapy (OR [odds ratio] 1.85, p = 0.028) or targeted immunotherapy (OR 4.71, $p < 0.001$) was associated with a higher HER2 change rate than chemotherapy alone. The median follow-up time was 31.2 months. HER2 expression changes were associated with worse PFS (HR [hazard ratio] 1.52, p = 0.040) and OS (HR 1.51, p = 0.043), with decreased HER2 expression showing the poorest PFS (Log-rank p = 0.030) and OS (Log-rank p = 0.025). Subgroup analysis showed in PR/SD group, HER2 expression changes was associated with significantly worse PFS (HR 2.48, p = 0.003) and OS (HR 2.56, p = 0.002), while no survival differences were observed in PD group. **Conclusions:** HER2 expression frequently changes during the treatment of gastric cancer, particularly after immunotherapy and targeted therapy, and is associated with worse survival outcomes. Dynamic HER2 testing contributes to guiding precision therapy for gastric cancer. Research Sponsor: None.

Tislelizumab (TIS; BGB-A317) plus chemotherapy (CT)/chemoradiotherapy (CRT) as positron emission tomography (PET)–guided neoadjuvant (n) treatment (tx) for resectable esophageal squamous cell carcinoma (R-ESCC): RATIONALE-213 final analysis.

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Background: Studies have shown overall survival improvements with nCRT + surgery vs surgery alone in locally advanced ESCC. However, preoperative CRT may have additional safety concerns, leading to some patients (pts) receiving nCT rather than nCRT. PET-computed tomography maximum standardized uptake value (SUV_{max}) change after induction CT (IC) has been shown to have reliable predictive value of pathological complete response (pCR) for R-ESCC in pts with nCRT and may optimize neoadjuvant tx selection. TIS (anti-PD-1) has improved survival in pts with ESCC. We report the final analysis of RATIONALE-213, a phase 2, open-label, multicenter study in China evaluating PET-guided nTIS + CT/CRT in R-ESCC (NCT04974047). **Methods:** Eligible adult pts had histologically confirmed R-ESCC (cT1-2N + M0 or cT3N any M0), ECOG performance status 0/1, adequate organ function, no fistula risk, and had received no prior tx. Pts had a baseline (BL) PET scan, 1 cycle of IC (cisplatin-paclitaxel [Cis-Pac]), and a PET scan 15-21 days later. Pts were grouped into 2 cohorts by response to IC based on the percentage decrease in 2nd PET SUV_{max} in the primary tumor: responders (R, ≥35%) or nonresponders (NR, < 35%). Both cohorts received 3 cycles of TIS 200 mg IV Q3W, the first 2 with CT (2 cycles Cis-Pac) for R, or with CRT (2 cycles investigator [Inv]-chosen CT [Cis-Pac, or 5-FU + Cis] + RT [40 Gy/20 fractions]) for NR, then surgery. Primary endpoint was pCR per local pathologist. Secondary endpoints were 1-year disease-free survival (DFS), 1-year event-free survival (EFS), objective response rate (ORR) before surgery, R0 resection rate by Inv, and safety. **Results:** Of 70 pts enrolled, 15 (21.4%), 48 (68.6%), and 7 (10.0%) had stage II, III, and IVA disease at BL, respectively. As of 25 Oct 2024 (median follow-up 25.5 mo), 30 pts were R and 40 NR. Of R, 20 (66.7%) had surgery. Of NR, 32 (80.0%) had surgery. Efficacy endpoints are shown in the table. Median DFS and EFS were not reached for R and NR. Grade ≥3 treatment-related adverse events (TRAEs) in R (15 [50.0%]) and NR (33 [82.5%]) were consistent with known CT or CRT toxicity; serious TRAEs occurred in 5 R (16.7%) and 7 NR (17.5%). No TRAEs led to surgery cancellation or death. **Conclusions:** APET-guided approach may help optimize neoadjuvant tx of R-ESCC. nTIS + CT/CRT showed promising efficacy and a tolerable safety profile in both responders and nonresponders. Clinical trial information: NCT04974047. Research Sponsor: BeOne Medicines Ltd.

	R	NR
pCR, [a] n (%)	6 (30.0)	11 (34.4)
(95% CI)	(11.9, 54.3)	(18.6, 53.2)
1-year DFS, [b] %	79.0	74.2
(95% CI)	(47.9, 92.7)	(53.3, 86.8)
1-year EFS, [c] %	87.1	67.8
(95% CI)	(64.3, 95.8)	(48.3, 81.2)
R0 resection, [a] n (%)	19 (95.0)	29 (90.6)
ORR, [d] n (%)	15 (71.4)	14 (42.4)

[a]Efficacy analysis set (EAS) R=20; NR=32.
[b]EAS with R0 resection R=19; NR=29.
[c]Safety analysis set (SAS) R=30; NR=40.
[d]SAS with measurable disease at BL R=21; NR=33.

Efficacy and safety of surufatinib (Sur) plus paclitaxel (Pac) as second line (2L) treatment for advanced gastric cancer (aGC): Final results from a phase 2 trial.

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Background: Standard chemotherapy (ChT) provides unsatisfactory efficacy for patients with aGC in the 2L setting. Recent studies have suggested improved efficacy with an antiangiogenic agent plus Pac. Although ramucirumab plus Pac have been approved as a 2L treatment, access to this combination regimen is limited in China. Sur is a potent VEGFRs, FGFR1 and CSF-1R inhibitor. This trial is aimed to assess the efficacy and safety of Sur plus ChT as a 2L treatment for aGC. Our previous report (ASCO-GI 24) revealed promising anti-tumor activity of this regimen. Now we are presenting the final analyses including long-term survival results. **Methods:** This single-arm, phase 2 clinical trial enrolled patients with HER2-negative aGC who had failed standard first-line treatment. Eligible patients received Sur (250mg, po, qd) plus Pac (150mg/m^2, iv, d1) at 21-day cycles for 6 cycles, followed by maintenance with single-agent Sur until disease progression or intolerable toxicity. Tumor responses were assessed every 6 weeks by investigators per RECIST v1.1. The primary endpoint was ORR, and secondary endpoints were DCR, PFS, OS, and safety. **Results:** As of Dec 20, 2024, of the 35 patients enrolled, median age was 65 (range: 33-75), 26 (74.3%) were male, 31 (88.6%) had an ECOG PS of 1, 12 (34.3%) had positive PD-L1 (defined as CPS ≥1), and 26 (74.3%) had received 1L immunotherapy (IO). Seven (20.0%) patients had primary GEJC, and all patients had stage IV disease, with lymph nodes (23, 65.7%), liver (16, 45.7%) and peritoneum (14, 40.0%) being the most common metastatic sites. Tumor response assessments were available in 32 patients, the ORR was 25.0% and DCR was 87.5%. Primary GEJC (42.9% vs 20.0%, *P*= 0.327) and baseline liver metastases (40.0% vs 11.8%, *P*= 0.106) seemed correlated to a better ORR, while baseline peritoneal metastases (8.3% vs 35.0%, *P*= 0.204) the reverse. With a median follow-up of 12.6 (95% CI: 10.4-14.9) months (mo), the mPFS was 5.7 (95% CI: 4.7-6.93) mo and the mOS was 10.8 (95% CI: 7.0-17.2) mo. Within the subgroup patients who had IO exposure in the 1L setting (n = 26), the ORR was 25.0%, the DCR was 91.7%, the mPFS was 5.9 (95% CI: 4.7-10.5) mo, and the mOS reached 14.4 (95% CI: 8.5-NR) mo. Treatment-related adverse events of grade ≥3 included neutropenia (40.0%), leukopenia (34.3%), hypertension (11.4%), and proteinuria (5.7%). There were no treatment-related serious adverse events or on-treatment deaths. **Conclusions:** These encouraging long-term efficacy results and the manageable safety profile suggested a preferable position of Sur plus Pac as the 2L treatment for aGC, notably, following the current standard 1L IO-containing regimens. Clinical trial information: ChiCTR2200063336. Research Sponsor: HUTCHMED.

A multicenter randomized phase II study of trastuzumab biosimilar (CT-P6) and chemotherapy (SOX or CapeOX) in HER2-positive advanced/recurrent gastric cancer (KSCC: TROX study).

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Background: The efficacy and safety of the trastuzumab biosimilar (CT-P6) combined with S-1/oxaliplatin (SOX) or capecitabine/oxaliplatin (CapeOX) were investigated in patients with HER2-positive advanced or recurrent gastric cancer who had not previously received chemotherapy. CT-P6 is a biosimilar of trastuzumab, which has demonstrated comparable safety and efficacy to trastuzumab in breast cancer. However, no clinical trials have evaluated CT-P6 in gastric cancer to date. **Methods:** This randomized, open-label, multicenter phase II study enrolled patients with HER2-positive unresectable or recurrent gastric cancer. Participants were randomized to receive SOX plus trastuzumab biosimilar therapy (S-1 orally, 40–60 mg twice daily for 14 days every 3 weeks, oxaliplatin intravenously at 130 mg/m^2 on day 1 every 3 weeks, and CT-P6 at 8 mg/kg on day 1 and 6 mg/kg every 3 weeks thereafter) or CapeOX plus trastuzumab biosimilar therapy (replacing S-1 with capecitabine [1,000 mg/m^2] as described above) until disease progression. The primary endpoint was overall response rate (ORR) in both arms, with a null hypothesis response rate set at 43%, the lower bound of the 90% confidence interval reported in previous trastuzumab trials. Secondary endpoints included progression-free survival (PFS), overall survival (OS), and safety. **Results:** Between May 2019 and November 2022, 67 patients were enrolled in the study. Patient characteristics were as follows: male/female ratio of 49/18, median age 68 years (range: 34–80), and performance status (PS) of 0/1 in 53/14 patients. The ORR was 76.1% (90% CI: 67.6–84.7%), with the lower limit of the confidence interval exceeding the threshold response rate of 43%, confirming the efficacy of trastuzumab biosimilar therapy. The one-year survival rate was 65.2% (95% CI: 49.8–78.6%), meeting the primary endpoint. The median OS was 18.7 months (90% CI: 15.1–23.1), and the median PFS was 9.0 months (90% CI: 6.5–10.7). Although the study was not designed to compare SOX and CapeOX, the response rate was slightly higher in the CapeOX group (81.3% [90% CI: 69.9–92.6%]) compared to the SOX group (71.4% [90% CI: 58.9–84.0%]). Similarly, OS was slightly better in the CapeOX group (22.3 months [90% CI: 15.1–42.1]) than in the SOX group (16.7 months [90% CI: 12.7–19.6]). The most frequent grade 3 or 4 adverse events were neutropenia (15.2%), appetite loss (12.1%), and diarrhea (7.6%). **Conclusions:** Trastuzumab biosimilar (CT-P6) combined with SOX or CapeOX demonstrated robust antitumor efficacy and manageable toxicity in patients with advanced or recurrent gastric cancer. Clinical trial information: jRCTs071190007. Research Sponsor: None.

Neoadjuvant serplulimab in combination with chemotherapy for locally advanced gastric or gastro-esophageal junction cancer.

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Background: Perioperative therapy combined with surgery is the standard treatment for locally advanced gastric or gastro-esophageal junction (G/GEJ) cancer; however, long-term survival remains suboptimal. Immunotherapy has demonstrated antitumor activity and an acceptable safety profile in advanced G/GEJ cancer. This study aimed to evaluate the efficacy and safety of neoadjuvant Serplulimab, a PD-1 inhibitor, in combination with chemotherapy in previously untreated, locally advanced G/GEJ cancer. **Methods:** Eligible patients with resectable G/GEJ adenocarcinoma staged as cT3-4aN+M0 were enrolled. The treatment regimen included Serplulimab (300 mg on day 1, every 3 weeks [Q3W]) plus SOX chemotherapy (oxaliplatin 130 mg/m^2 on day 1; and S-1 60 mg twice daily on days 1-14, Q3W) for three cycles. Following the preoperative treatment, patients underwent surgery 6-8 weeks after the therapy. The primary endpoint was pathological complete response (pCR) rate. Secondary endpoints included major pathological response (MPR) rate, R0 resection rate, disease-free survival (DFS), overall survival (OS), and toxicity. **Results:** From October 13, 2023, to December 31, 2024, 25 patients were enrolled, all of whom completed neoadjuvant therapy and underwent radical surgical. The R0 resection rate was 100%. Five patients achieved pCR (pCR rate: 20%), and an additional five patients achieved MPR (MPR rate: 40%). Median DFS and OS were not reached. Safety analysis included all patients who received at least one cycle of neoadjuvant therapy. The most common treatment-related adverse events (TRAEs) of any grade included nausea, anorexia, thrombocytopenia, fatigue, and thyroid dysfunction. No grade ≥3 TRAEs were observed. **Conclusions:** Neoadjuvant Serplulimab combined with SOX chemotherapy demonstrated promising efficacy and a favorable safety profile in patients with locally advanced, resectable G/GEJ adenocarcinoma. These findings support the potential role of immune-based neoadjuvant therapy in this setting. Research Sponsor: None.

Safety, efficacy, and biomarker analysis from a phase II trial of intensive chemotherapy combined with serplulimab and trastuzumab in patients with advanced HER2-positive gastric cancer.

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Background: Keynote-811 has proven the efficacy of combined PD-1 and HER2 blockade with chemotherapy in HER2-positive gastric cancer. Our study aims to enhance the survival of patients by replacing standard chemotherapy with intensive chemotherapy and conducting biomarker analysis. **Methods:** This prospective, single-arm, open-label study was carried out across five centers in China, recruiting patients (pts) with unresectable locally advanced or metastatic HER2-positive gastric cancer. Pts receive Serplulimab (4.5 mg/kg, D1, Q3W), Trastuzumab (initial 8 mg/kg, D1, then 6 mg/kg, D1, Q3W), and the DOS regimen: oxaliplatin (100 mg/m^2, IV), docetaxel (40 mg/m^2, IV), and S-1 (40-60mg, BID, D1-14, Q3W). Chemotherapy is up to 8 cycles. Serplulimab and Trastuzumab can be administered until tumor progression. Gastroscopic biopsy was taken before the treatment and dynamic blood samples were collected at C1D1 (T0), C2D1 (T1) and C7D1 (T2) for biomarker analysis. Genomic DNA from tumor tissue and circulating tumor DNA (ctDNA) underwent targeted DNA sequencing containing 571 genes. **Results:** From July 2022 to September 2024, 40 pts were recruited. The median follow-up was 7.9 months. There were 10 females and 30 males, with a median age of 59 (31-74). 37 pts were eligible for efficacy assessment. The objective response rate (ORR) was 92% (95% CI: 0.87, 0.96), with a complete response rate of 3% (95% CI: 0, 0.05), and a partial response rate of 89% (95% CI: 0.84, 0.94). Median progression free survival has not been reached. 38 pts (95%) experienced adverse events (AEs) of any grade. Grade 3 or above AEs occurred in 14 pts (35%), 2 pts with grade 4 AEs (1 with thrombocytopenia and 1 with myelosuppression). No grade 5 events were observed. The most common AEs were anemia (35%), neutropenia (23%), nausea and vomiting (20%) and leukopenia (20%). 15 (38%) pts had dose interruptions due to AEs, with no treatment discontinuation. HER2 CNV gain was detected in 82.1% (23/28) of tissue samples and 74.3% (26/35) of ctDNA samples. In matched ctDNA and tissue samples (N = 26), 88.5% (23/26) showed concordant HER2 CNV gain results. Elevated tissue HER2 CNV were associated with more pronounced tumor shrinkage (R = -0.35, P = 0.073). Plasma HER2 gain detection rate decreased from 79.1% (19/24) at T0 to 16.7% (4/24) at T1 ($P < 0.001$). Similar results were observed from T0 to T2 ($P < 0.001$). **Conclusions:** This regimen demonstrated remarkable efficacy with a high ORR and manageable toxicity. Tumor HER2 CNV and ctDNA dynamic monitoring correlated with treatment efficacy. The subsequent results of biomarker analysis will be presented at the upcoming conference. Clinical trial information: NCT05311189. Research Sponsor: None.

Pts characteristics.

	N=40
Age, ≥65 years	38%
Male	75%
PD-L1 status	
CPS ≥1	65%
CPS <1	13%
Unknown	22%
HER2 status	
IHC 2+ ISH positive	25%
IHC 3+	75%
Primary gastrectomy or esophagectomy	
Yes	15%
No	85%
Metastatic sites	
0–2	60%
≥3	40%

First-line osemitamab (TST001) plus nivolumab and CAPOX for advanced G/GEJ cancer (TranStar102): Updated results of cohort G from a phase I/IIa study.

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Background: Claudin 18.2 (CLDN18.2) is a clinically validated therapeutic target and has been broadly explored with different modalities in gastric/gastroesophageal (G/GEJ) cancer treatment. Osemitamab is a humanized monoclonal antibody with improved affinity to CLDN18.2, reduced fucosylation and enhanced ADCC activity and has been observed to upregulate PD-L1 expression on CLDN18.2-positive tumor cells. *In vivo* anti-tumor activity of combination of osemitamab plus an anti-PD-1/PD-L1 antibody and chemotherapies was significantly stronger than any of the doublet combinations, regardless of the PD-L1 CPS levels, making the triple combination of osemitamab, nivolumab and CAPOX an attractive combination to explore. **Methods:** Cohort G from TranStar102 (NCT04495296, a phase I/II study) was designed to evaluate the safety and preliminary efficacy of osemitamab at two dose levels (3mg/kg or 6mg/kg Q3W) plus nivolumab and CAPOX as the first-line treatment in patients with G/GEJ cancer. 40 patients were planned to be enrolled in each dose level. Key eligible criteria included HER2 negative or unknown, unresectable locally advanced or metastatic G/GEJ cancer, regardless of CLDN18.2 or PD-L1 expression and treatment naïve for advanced disease. The endpoints include safety, efficacy, PK and predictive value of the different levels of CLDN18.2 expression, etc. **Results:** As of Jan 13, 2025, 82 patients were dosed with osemitamab plus nivolumab and CAPOX (40 at 3mg/kg, 42 at 6mg/kg) with median follow-up of 21.3 months. All patients experienced treatment-related adverse events (TRAEs). The safety profile was similar with the previously presented data (2024 ESMO poster), and the most commonly observed TRAEs were on-target and off-tumor toxicities, such as nausea, vomiting and hypoalbuminemia, and were manageable. 44 out of 82 patients had confirmed partial response and the objective response rate (ORR) was 55.7%. There was a clear trend between anti-tumor efficacy and CLDN18.2 expression, with a confirmed ORR of 68% and median progression-free survival of 16.6 months (95% CI: 5.8, 21.7) for the patients with CPS known and CLDN18.2 high/medium expression (defined as CLDN18.2 membranous staining ≥2+ in ≥40% of tumor cells by immunohistochemistry in the central laboratory) (n=26). By the cut-off date, there were 33 patients in survival follow-up including 12 patients still with ongoing treatment. The median overall survival was 20.4 months (95% CI:15.0, NE) for all the 82 patients. Updated clinical data and details by biomarkers levels will be reported at the time of conference. **Conclusions:** The updated data indicate that the combination of TST001 plus nivolumab and CAPOX for the first-line treatment of patients with G/GEJ cancer is safe and well tolerated with encouraging durable PFS and survivals, especially for the patients with high/medium CLDN18.2 expression. Clinical trial information: NCT04495296. Research Sponsor: Suzhou Transcenta Therapeutics Co, Ltd.

Real-world analyses to evaluate the role of TIGIT as a target in first-line (1L) gastric, gastroesophageal junction, and esophageal adenocarcinomas (GC/GEJC/EAC).

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Background: Anti-programmed death protein 1 (PD-1) immune checkpoint inhibitors (ICIs) are approved for GC/GEJC/EAC.T-cell immunoreceptor with Ig and ITIM domains (TIGIT) is a potential anti-tumor ICI target.Understanding how PD-L1 (*CD274*), effector T-cell (Teff), and *TIGIT* RNA expression levels correlate with real-world outcomes of 1L treatment can inform the potential for TIGIT as a target. **Methods:** Deidentified real-world data for patients (pts) with metastatic GC/GEJC/EAC were included from the Tempus AI, Inc. clinicogenomic database. Data were analyzed for pts with available longitudinal clinical data and biopsies (whole transcriptome RNA-sequencing [seq], 648 gene panel DNA-seq, and PD-L1 immunohistochemistry). Gene expression comparisons, including between *TIGIT* and a Teff gene set (geometric mean of *CD8A*, *GZMA*, *GZMB*, *IFNG*, *EOMES*, and *PRF1*), used the Wilcoxon test, Kruskal-Wallis test, and Spearman correlation. Real-world time to next treatment or death (rwTTNTD; maximum follow-up 24 months) was assessed for 1L ICI + chemotherapy (chemo) or chemo using the Kaplan-Meier method and compared by expression level (high [$\geq$ median] vs low [$<$ median]) of *TIGIT*, Teff gene set, and *TIGIT* normalized by Teff gene set. **Results:** Among 545 pts (1L ICI + chemo, n = 50; 1L chemo, n = 124) *TIGIT* expression was most highly correlated with Teff (R = 0.80, $P < 0.001$) and *FOXP3* expression (R = 0.78, $P < 0.001$), followed by *CD274* expression (R = 0.57, $P < 0.001$). Positive correlations with PD-L1 combined positive score were observed for *TIGIT* and Teff expression ($P < 0.001$ for both) but not *TIGIT* normalized to Teff levels ($P > 0.05$). Biopsies from liver metastases, which tend to show a poor response to ICIs, had lower immune signatures vs stomach tumor biopsies ($P < 0.001$). High vs low expression of *TIGIT* and Teff were associated with numerically longer rwTTNTD for ICI + chemo, with HRs (95% CI) of 0.82 (0.43–1.54) for *TIGIT* (n = 29 vs 21) and 0.78 (0.42–1.48) for Teff (n = 28 vs 22). Corresponding HRs (95% CI) for chemo were 1.04 (0.70–1.54) for *TIGIT* (n = 53 vs 71) and 1.26 (0.85–1.87) for Teff (n = 64 vs 60). When *TIGIT* expression was normalized to Teff levels, HRs (95% CI) for rwTTNTD for high vs low expression were 0.92 (0.49–1.71) for ICI + chemo (n = 23 vs 27) and 0.81 (0.54–1.20) for chemo (n = 57 vs 67). **Conclusions:** *TIGIT* expression was highly correlated with *FOXP3* and Teff gene set expression in GC/GEJC/EAC tumors. The improved rwTTNTD seen in pts with high *TIGIT* expression may be driven by these patients also having high Teff expression. When *TIGIT* is normalized to Teff, pts with high *TIGIT* expression lose this added benefit. Combining anti-TIGIT and anti–PD-1 treatments may lead to enhanced T cell activation, which could bring benefit to pts with 1L GC/GEJC/EAC. Larger studies will help confirm these findings. Research Sponsor: Gilead Sciences, Inc.

Distinct microenvironment phenotypes across tumor, vascular, and immune compartments from ramucirumab plus pembrolizumab in refractory gastric cancer: A phase II trial.

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Background: Combining immune checkpoint inhibitor (ICI) with vascular endothelial growth factor (VEGF)/VEGF receptor inhibition has yielded promising results in multiple tumor types. This phase II trial investigated the efficacy and molecular mechanisms of ramucirumab plus pembrolizumab in refractory gastric cancer patients. **Methods:** We conducted a prospective phase II single-arm trial of ramucirumab plus pembrolizumab as salvage treatment in patients with metastatic GC who failed to respond to standard fluoropyrimidine plus platinum with or without programmed cell death protein 1 (PD-1) inhibitors. Eligible patients had programmed death-ligand 1 (PD-L1) combined positive score more than five. The primary objective was to objective response rate (ORR) and secondary end points included disease control rate, duration of response, progression-free survival and overall survival, and toxicity. Comprehensive molecular profiling, including Digital Spatial Profiling, and mass cytometry was performed on tumor samples and peripheral blood. **Results:** Twenty-six patients were enrolled in this study between June 2021 and May 2023. No patient attained complete response (CR), while 6 patients achieved confirmed partial response (PR), resulting in a response rate (RR) of 23.1% (95% CI, 4.06–34.4). The median PFS for all patients was 2.7 months (95% CI, 1.84 - 3.56 months), and median OS was 10.9 months (95% CI, 2.31 – 18.29). Grade $\geq$ 3 treatment-related adverse events occurred in 38.5 % of patients. Digital Spatial Profiling revealed distinct tumor microenvironment (TME) phenotypes between responders and non-responders. Responders had high CTL infiltration and vascular normalization in their tumor specimen after treatment which led to favorable treatment outcome. In support of this, spatial profiling revealed the shortest median distance between immune cells and vessels, suggesting enhanced transendothelial migration of immune cells. Nonresponders had significantly upregulated TGF-β pathway and low tumor vascularity. On-treatment analysis demonstrated a shift towards increased immune cell infiltration and decreased tumor cellularity. Mass cytometry of peripheral blood revealed lower proportions of myeloid-derived suppressor cells in responders. **Conclusions:** Ramucirumab+pembrolizumab showed modest clinical efficacy, with manageable toxicity and durable responses. Although limited to a small subset of patients, a few patients who had previously responded to ICI benefited from ramucirumab+pembrolizumab. Clinical trial information: NCT0005753. Research Sponsor: None.

GABRP as a biomarker for predicting anti-PD1 therapeutic efficacy in advanced gastric cancer (WJOG10417GTR study).

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Background: GABRP, Gamma-aminobutyric acid type A receptor subunit π, is a key molecule that influences tumor properties and patient prognosis in various cancers, including gastric cancer (GC): GABRP is significantly upregulated in tumor tissues, and promotes tumor progression and metastasis via chemokine signaling and macrophage recruitment, leading to poor prognosis. Thus, GABRP seems to be a promising potential target for cancer treatment. However, it remains unclear whether the GABRP-targeting strategy can contribute to GC treatment, especially anti-PD1/PDL1 therapy, which has recently attracted great attention. **Methods:** We collected biopsy tumor tissues from 96 patients with advanced GC before and one month after nivolumab monotherapy in the WJOG10417GTR study according to the protocol (No. 2017-473) approved by the IRB, and analyzed for GABRP expression by RNA-sequencing (RNAseq) and immunohistochemical staining (IHC; only at pre-treatment). Progression-free survival (PFS) and overall survival (OS) were compared between high and low groups divided by the cutoff value determined by change point of the larger log hazard ratios (HRs) based on the method for modeling continuous-scale covariates. This study was supported by Ono Pharmaceutical and Bristol Myers Squibb. **Results:** RNAseq data revealed that high levels of GABRP gene expression in tumors at baseline were significantly associated with shorter PFS (median PFS [mPFS] 1.643 months [95% CI = 1.281 - 3.253] vs 3.170 months [1.971 - 10.251], HR = 2.798, P = 0.005) and shorter OS (median mOS [mOS] 5.092 months [3.450 - NA] vs 15.409 months [13.733 - NA], HR = 5.145, $P < 0.001$), and the high post-treatment levels were significantly associated with shorter PFS (mPFS 1.873 months [1.511 - 3.253] vs 4.123 months [2.073 - NA], HR = 3.333, P = 0.009) and shorter OS (mOS 7.162 months [5.092 - 15.310] vs NA [13.733 - NA], HR = 4.524, P = 0.015), as compared to low levels. This was confirmed by IHC data that showed similar results, albeit only baseline data: patients with high baseline levels of GABRP protein expression in tumors had significantly shorter PFS (mPFS 1.528 months [0.986 - 1.971] vs 3.121 months [1.873 - 4.238], HR = 1.727, P = 0.016). **Conclusions:** These results suggest that GABRP expressed in tumors is a significant poor prognostic factor for nivolumab monotherapy in advanced GC. GABRP may be a promising biomarker for predicting anti-PD1/PDL1 therapeutic efficacy in advanced GC, and targeting it may contribute to improving the clinical outcomes in GC as a new therapeutic strategy. Research Sponsor: Ono Pharmaceutical and Bristol Myers Squibb.

KEYNOTE-859: 4.5-year median follow-up of pembrolizumab plus chemotherapy for previously untreated advanced HER2-negative gastric or gastroesophageal junction (G/GEJ) adenocarcinoma.

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Background: In the phase 3KEYNOTE-859 study (NCT03675737), first-linepembrolizumab (pembro) + chemotherapy (chemo) continued to provide longer OS (HR, 0.79; 95% CI, 0.71-0.88) and PFS (HR, 0.76; 95% CI, 0.68-0.85), and a higher ORR (51.0% vs 42.0%) vs placebo + chemo in participants (pts) with HER2-negative G/GEJ adenocarcinoma, after a median follow-up of 41.6 mo (August 22, 2023). We present results after an additional 13 mo of follow-up. **Methods:** Eligible pts with untreated locally advanced or metastatic HER2-negative G/GEJ adenocarcinoma with PD-L1 status, measurable disease, and ECOG PS 0 or 1 were randomly assigned 1:1 to receive pembro 200 mg or placebo IV Q3W for ≤35 cycles + investigator's choice of chemo (5-FU + cisplatin [FP] vs capecitabine + oxaliplatin [CAPOX]). The primary end point was OS. Secondary end points included PFS, ORR, and DOR, all per RECIST v1.1 by BICR, and safety. The data cutoff was September 27, 2024. **Results:** Median follow-up was 54.8 mo (Q1-Q3, 46.8-62.1). In all randomly assigned pts in the intention-to-treat population (N = 1579), median OS was 12.9 mo (95% CI, 11.9-14.0) for pembro + chemo vs 11.5 mo (95% CI, 10.6-12.1) for placebo + chemo (HR, 0.78; 95% CI, 0.70-0.86). In pts with PD-L1 CPS ≥1, median OS was 13.0 mo (95% CI, 11.6-14.2) vs 11.4 mo (95% CI, 10.5-12.0; HR, 0.74 [95% CI, 0.66-0.84]). In pts with PD-L1 CPS ≥10, median OS was 15.8 mo (95% CI, 14.0-19.3) vs 11.8 mo (95% CI, 10.3-12.7; HR, 0.64 [95% CI, 0.53-0.77]). PFS, ORR, and DOR were also consistent between the intention-to-treat population and pts with PD-L1 CPS ≥1 and PD-L1 CPS ≥10 (Table). Treatment-related AEs were reported in 751 pts (95.7%; grade 3-5, 466 [59.4%]) for pembro + chemo and 736 (93.5%; grade 3-5, 404 [51.3%]) for placebo + chemo. **Conclusions:** Pembro + chemo continued to show improved OS, PFS, and ORR vs placebo + chemo after a median study follow-up of 54.8 mo, regardless of PD-L1 status. The findings further support pembro + chemo as a first-line treatment option for locally advanced or metastatic HER2-negative G/GEJ adenocarcinoma. Clinical trial information: NCT03675737. Research Sponsor: None.

	All pts N = 1579		PD-L1 CPS ≥1 n = 1235		PD-L1 CPS ≥10 n = 553	
	Pembro + chemo n = 790	Pbo + chemo n = 789	Pembro + chemo n = 618	Pbo + chemo n = 617	Pembro + chemo n = 280	Pbo + chemo n = 273
OS, median (95% CI), mo	12.9 (11.9-14.0)	11.5 (10.6-12.1)	13.0 (11.6-14.2)	11.4 (10.5-12.0)	15.8 (14.0-19.3)	11.8 (10.3-12.7)
HR (95% CI)	0.78 (0.70-0.86)		0.74 (0.66-0.84)		0.64 (0.53-0.77)	
PFS, median (95% CI), mo	6.9 (6.3-7.2)	5.6 (5.5-5.7)	6.9 (6.0-7.2)	5.6 (5.4-5.7)	7.8 (6.8-8.5)	5.6 (5.4-6.7)
HR (95% CI)	0.76 (0.68-0.85)		0.72 (0.64-0.82)		0.62 (0.51-0.76)	
ORR, % (95% CI)	51.1 (47.6-54.7)	42.0 (38.5-45.5)	51.9 (47.9-55.9)	42.6 (38.7-46.6)	60.4 (54.4-66.1)	43.2 (37.3-49.3)
DOR, median (range), mo	8.0 (1.2+ to 66.3+)	5.7 (1.3+ to 58.1+)	8.3 (1.2+ to 66.3+)	5.6 (1.3+ to 58.1+)	10.0 (1.2+ to 66.3+)	5.7 (1.4+ to 55.0+)

Co-expressing pattern of multiple biomakers and dynamic change of Claudin18.2 expression after systemic chemotherapy in advanced gastric cancer.

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Background: Gastric cancer (GC) is a heterogeneous disease classified by Lauren classification and TCGA's four molecular subtypes. Targeting Claudin (CLDN)18.2 has emerged as a promising therapy. However, a comprehensive understanding of CLDN18.2 in advanced GC, its clinicopathologic correlations, and prognostic significance remains limited. We analyzed the co-expression of multiple biomarkers and dynamic changes in CLDN18.2 following systemic chemotherapy. **Methods:** This retrospective study included 402 patients with stage IV GC at Yonsei Cancer Center (2015–2023) treated with palliative doublet chemotherapy. Paired pre- and post-treatment tissues were available for 124 patients. CLDN18.2 expression was assessed using the VENTANA CLDN18 (43-14A) RxDx Assay, with positivity defined as ≥75% of tumor cells. HER2, EBV, dMMR, and PD-L1(22C3) were also evaluated by immunohistochemistry. Overall survival (OS) was estimated using the Kaplan-Meier method, and a log-rank test was performed to compare survival according to CLDN18.2 positivity. **Results:** The CLDN18.2 positivity rate was 30.6%, consistent with previous reports. It was slightly higher in HER2-negative (31.5%) than HER2-positive (27.3%) ($p = 0.44$). CLDN18.2 positivity was significantly higher in EBV-positive than negative (63.6% vs 29.4%, $p < 0.05$) and in pMMR versus dMMR (31.7% vs 9.5%, $p < 0.05$). Regarding PD-L1 status, the positivity rate was higher in the PD-L1 negative compared to the positive by CPS 1(36.1% vs 25.8%, $p < 0.05$). We observed that CLDN18.2 expression seems to be decreasing with higher PD-L1 expression (28.5 % in patients with CPS ≥5, 24% in CPS ≥10). The OS (median months, 95% CI) based on CLDN 18.2 expression was similar [22.5 (18.6-25.2) vs 23.2 (17.9-27.4) in CLDN18.2 positive group], regardless of HER2 status. Among 124 patients with paired samples, pre-treatment CLDN18.2 positivity was 22.8%, increasing to 36.5% post-treatment. The increase was more pronounced in HER2 negative (39.0%) compared to positive (29.5%). Notably, 79.9% of patients showed consistent CLDN18.2 expression between pre- and post-treatment samples, while 20.1% demonstrated changes in expression. These changes were not associated with other markers such as HER2, EBV, dMMR, or PD-L1. **Conclusions:** Higher CLDN18.2 positivity rates in specific subgroups, such as pMMR and PD-L1 negative, suggest the potential role of anti-CLDN therapy in these subgroups. This study also highlights the dynamic changes of CLDN18.2 expression in advanced gastric cancer, with an increase observed after first-line systemic treatment in a subset of patients. Further studies should focus on prospective analyses and stratify changes in CLDN18.2 expression by treatment regimen to better understand its role as a therapeutic target and its implications for treatment resistance and disease progression. Research Sponsor: None.

Camrelizumab plus albumin-bound paclitaxel and S-1 as first-line treatment of HER-2 negative unresectable locally advanced or advanced gastric and gastro-esophageal junction adenocarcinoma: A phase II clinical trial.

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Background: Gastric cancer is a common malignant tumor of the digestive tract. For nearly 90% of HER2 negative advanced gastric and gastroesophageal junction adenocarcinoma (G/GEJ) patients (pts), the current first-line treatment options and efficacy are limited, and new therapeutic drugs are urgently needed to improve the efficacy of advanced G/GEJ. **Methods:** This is a prospective, single center, single arm, open label phase II clinical trial involving HER-2 negative G/GEJ diagnosed by histopathology. Pts received 4-6 cycles of treatment with camrelizumab combined with albumin bound paclitaxel and S-1, followed by camrelizumab maintenance therapy until progression or 2 years. By following up with pts and evaluating clinical efficacy based on imaging examinations, the effectiveness and safety of the protocol can be assessed. **Results:** From December 2020 to December 2024, a total of 47 pts obtained informed consent based on exclusion criteria. As of the deadline (January 6, 2025), the average follow-up period was 17.4 months, with a median follow-up time of 16.7 months (range: 1.6-42.2 months). One patient had completed 2 years of treatment and ended maintenance therapy with camrelizumab, 5 pts (12.5%) were still receiving treatment, 34 pts (85.0%) stopped treatment, and 28 pts (70%) developed disease progression (PD). The best therapeutic effect was achieved in 2 cases with CR, 25 cases with PR, 11 cases with SD, and 2 cases with PD. The experiment reached the primary endpoint with an ORR of 67.5%. The secondary endpoint DCR was 95.0%, the median PFS was 7.8 months [95% confidence interval (CI): 6.2-9.4 months], and the median OS was 23.8 months [95% confidence interval (CI): 15.2-32.4 months]. For all study subjects, there was no correlation between OS, PFS, and baseline characteristics of the study (age, gender, ECOG, microsatellite status, mismatch repair protein status, EBER status, PDL1 level, number of metastatic sites, presence of liver metastasis, presence of lung metastasis, presence of abdominal metastasis, presence of bone metastasis). Among all enrolled pts, 36 experienced adverse events (76.6%) and 18 experienced grade 3-4 TRAE (38.3%), mainly bone marrow suppression and immune related rash. **Conclusions:** As the first-line treatment for HER-2 negative advanced gastric and gastroesophageal junction adenocarcinoma, the combination of Carilizumab with albumin bound paclitaxel and S-1 has shown encouraging efficacy. Clinical trial information: ChiCTR2300069672. Research Sponsor: None.

4039 Poster Session

Efficacy and safety of LM-302 (anti-claudin 18.2 ADC) in combination with anti-PD-1 therapy for advanced gastric, gastroesophageal junction cancer and esophageal adenocarcinoma: Early-phase study results.

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Background: Claudin 18.2 (CLDN18.2), a tight junction protein highly expressed in gastric and gastroesophageal junction (GEJ) cancers, has emerged as a promising therapeutic target. LM-302 (tecotabart vedotin), a novel and potent MMAE-based ADC targeting CLDN18.2, has shown promising efficacy and safety as monotherapy in heavily pretreated advanced gastric cancer. This pooled analysis evaluates the efficacy and safety of LM-302 in combination with the anti-PD-1 antibody toripalimab as a first-line treatment option for patients with gastric, GEJ, or esophageal adenocarcinoma (EAC). **Methods:** Eligible patients with histologically confirmed, previously untreated, unresectable, HER2-negative gastric, GEJ, or EAC were included. Patients received LM-302 (1.6 mg/kg Q3W, 2.0 mg/kg Q3W or 1.8 mg/kg Q2W) and toripalimab (240 mg Q3W or 3 mg/kg Q2W). Endpoints included safety, objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), OS, and biomarker analysis. Data cutoff: January 7, 2025. **Results:** A total of 43 gastric, GEJ, or EAC patients (median age: 62.3 years; 65.1% male) from Australia and China were treated. No dose-limiting toxicities (DLT) were observed across all these dose levels. Treatment-related adverse events (TRAEs) related to LM-302 were reported in 39 patients (90.7%), with common events (≥20%) including anemia, decreased white blood cell count, decreased neutrophil count, increased aspartate transaminase (AST), vomiting, loss of appetite, and nausea. Grade ≥3 TRAEs related to LM-302 occurred in 16 patients (37.2%), the most common events (≥5%) were decreased neutrophil count (14.0%), increased alanine transaminase (11.6%), increased AST (9.3%), and anemia (7.0%). Among 41 efficacy-evaluable patients (median follow-up: 6.01 months), ORR was 65.9% (95% CI: 49.4-79.9%), and DCR was 85.4% (95% CI: 70.8- 94.4%). In 32 GC patients with CLDN18.2 expression in ≥25% of tumor cells (IHC 2+/3+), ORR was 71.9% (95% CI: 53.3-86.3%) and DCR was 96.9% (95% CI: 83.8-99.9%). Among these patients, ORR was 63.3% (95% CI: 35.1-87.2%) for patients with PD-L1 CPS $<$ 1 and 77.8% (95% CI: 52.4-93.6%) for patients with PD-L1 CPS ≥1. Median PFS and OS were not reached; one patient with PD-L1 CPS $<$ 1 achieved PR and remained on treatment for 14.70 months. **Conclusions:** LM-302 combined with toripalimab demonstrated encouraging anti-tumor activity and manageable safety as first-line treatment for patients with CLDN18.2-positive gastric, GEJ, and EAC, including those with low-to-moderate CLDN18.2 expression. These findings support further large-scale clinical trials to confirm efficacy, safety and clinical utility. Clinical trial information: NCT05188664; NCT05934331. Research Sponsor: LaNova Medicines Limited.

Efficacy and safety results of a multi-center phase II study of utidelone injection in combination with PD-1 inhibitor and chemotherapy for the first-line treatment of advanced gastric and esophagus cancers.

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Background: Utidelone is a novel microtubule inhibitor that offers several advantages including improved efficacy and safety, broader anti-cancer spectrum, blood-brain barrier penetrance, and response against multidrug-resistant tumors. Utidelone injection (UTD1) has been approved for advanced breast cancer in China. Previous studies have shown that utidelone monotherapy is effective for advanced gastric and gastroesophageal junction adenocarcinoma (GC) and esophageal squamous cell carcinoma (ESCC). This phase II study further explored the efficacy and safety of utidelone in combination with PD-1 inhibitor and chemotherapy for the 1^{st} line treatment of advanced GC and ESCC. **Methods:** Eligible patients were recruited into the two cohorts of metastatic and/or unresectable HER2 negative GC or ESCC, receiving utidelone ($30mg/m^2$/day iv on days 1–5 every 21-day) plus sintilimab (200 mg iv Q3W) and oxaliplatin ($130 mg/m^2$/day Q3W for up to 6 cycles), or utidelone ($30mg/m^2$/day iv on days 1–5 every 21-day) plus tislelizumab (200 mg iv Q3W) and capecitabine ($2000mg/m^2$/day po on days 1–14 every 21-day), respectively, until disease progression or unacceptable toxicity. The primary endpoint is ORR and second endpoints are CBR, PFS and safety. **Results:** The enrolment has been completed for both cohorts from April 2023 to October 2024. There were 27 eligible patients enrolled in the GC cohort with median age of 60 years (range 34-70), 6 females and 21 males. 23 patients were evaluable for efficacy with an outcome of 11 confirmed PRs and 12 SDs including 4 unconfirmed PR, and 5 patients were still receiving treatment (1-23 cycles). The confirmed ORR was 47.8% and CBR was 100%. The mPFS was $>$ 5.3 months. The most common $\geq$Grade 3 TEAEs included diarrhea (25.93%), neutropenia (14.81%), vomiting (14.81%), peripheral sensory neuropathy (11.11%), anemia (11.11%) and leukopenia (11.11%). Other AEs were all Grade 1 or 2, with no treatment-related deaths. There were 20 eligible patients enrolled in the ESCC cohort with median age of 61.5 years (range 47-70), 5 females and 15 males. 18 patients were evaluable for efficacy with an outcome of 6 confirmed PRs and 12 SDs, and 6 patients were still receiving treatments (1-12 cycles). The confirmed ORR was 33.3% and CBR was 100%. TEAEs $\geq$Grade 3 occurred in 8 patients including hypokalemia, lymphopenia/leukopenia, peripheral sensory neuropathy, hiccup, rash, pain, hypotension and anemia with one occurrence for each (5.5%). Other AEs were all Grade 1 or 2, with no treatment-related deaths. **Conclusions:** Utidelone plus PD-1 inhibitor and chemotherapy demonstrated promising efficacy and acceptable safety as first-line treatment for advanced GC and ESCC. There are 11 patients still on the study receiving continuous treatment. The final data will be provided at the time of presentation. Clinical trial information: NCT04911907. Research Sponsor: Beijing Biostar Pharmaceuticals Co., Ltd.

Fruquintinib in combination with camrelizumab and paclitaxel liposome and nedaplatin as first-line treatment for advanced esophageal squamous cell carcinoma (ESCC): A single-arm, phase II study.

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Background: Previous studies have indicated a synergistic effect of fruquintinib in combination with chemotherapy or immunotherapy. Therefore, we conducted a phase II study to evaluate the efficacy and safety of fruquintinib plus camrelizumab, paclitaxel liposome, and nedaplatin as a first-line treatment for advanced esophageal squamous cell carcinoma (ESCC). **Methods:** This study consisted of a dose-finding and a dose-expansion phase. A total of 33 to 36 eligible patients with untreated advanced ESCC were planned for enrollment. In the dose-finding phase, based on a standard 3+3 design, patients were treated with fruquintinib (3 mg, 4 mg, 5 mg, days 1-14, every 3 weeks, respectively, the initial fruquintinib dose was 4mg), in combination with a fixed dose of camrelizumab 200 mg, paclitaxel liposome 135 mg/m^2, and nedaplatin 70 mg/m^2 on day 1, every 3 weeks. In the dose-expansion phase, patients received camrelizumab, paclitaxel liposome, nedaplatin and recommended phase 2 dose (RP2D) of fruquintinib. A maximum of six cycles was administered, followed by maintenance therapy with fruquintinib in combination with camrelizumab. The primary endpoint was objective response rate (ORR). Secondary endpoints included disease control rate (DCR), progression-free survival (PFS), and safety. **Results:** As of December 28, 2024, 22 patients (20 males) were enrolled with a median age of 65 years (range 50-76). Among the 21 patients with metastases, 19.0% (4/21) had a single metastatic site and 81.0% (17/21) had multiple metastatic sites. In the dose-finding phase, no DLTs occurred in 3 patients at 4 mg and 6 patients at 5 mg, establishing fruquintinib's RP2D as 5 mg. Of the 19 patients evaluable for efficacy, 13 achieved a partial response, and 6 had stable disease. The confirmed ORR was 68.4% (95% CI: 47.5%-89.3%) for all evaluable patients and 68.8% (95%CI: 41.3%-89.0%) for patients receiving 5 mg dose of fruquintinib. The confirmed DCR was 100.0% (95%CI: 82.4%-100.0%). At a median follow-up of 5.1 (95%CI: 4.2-7.2) months, the median PFS was 8.7 (95%CI: 5.2-not available [NA]) months, the 6-month PFS rate reached 81.7%. The most common treatment-related adverse events (TRAEs) were anemia 72.7% (16/22), neutropenia 40.9% (9/22), leukopenia, hypertension 31.8% (7/22). Grade≥3 TRAEs were identified in seven patients, including neutropenia 13.6% (3/22), leukopenia 13.6% (3/22), oral mucositis 9.1% (2/22), nausea 4.5% (1/22), vomiting 4.5% (1/22), headache 4.5% (1/22), and anemia 4.5% (1/22). No treatment-related serious adverse events (TRSAEs) or deaths occurred. **Conclusions:** The combination of fruquintinib, camrelizumab, paclitaxel liposome, and nedaplatin demonstrated significant efficacy and manageable toxicity profile as a first-line treatment for advanced ESCC, suggesting a potential new treatment strategy. Clinical trial information: NCT06010212. Research Sponsor: None.

4043 Poster Session

Immune checkpoint inhibition in EBV-associated gastric cancer: A multi-center international retrospective analysis.

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Background: Epstein-Barr virus associated gastric cancer (EBVaGC) is found in ~9% of GC and is associated with a unique immunophenotype. Prior studies suggest 15-100% objective response rates (ORR) to immune checkpoint inhibition (ICI), but survival outcomes are limited by small cohort size. This study sought to clarify outcomes of ICI in EBVaGC across 9 global tertiary cancer centers, evaluate if next-generation sequencing (NGS) can replace EBER ISH as the gold standard for detection, and identify molecular features of ICI-responsive EBVaGC. **Methods:** Retrospective data were collected on patients (pts) with metastatic EBVaGC and stratified into patients receiving ICI alone or with chemotherapy, and by 1L vs. 2L+. Progression-free survival (PFS) and overall survival (OS) were analysed using the Kaplan-Meier method and were calculated from the start of treatment to the date of progression or death for PFS, and last follow up or death for OS. Cox regression model stratified by regions was used to examine factors associated with PFS. EBV viral reads were detected by NGS using independent cohorts by MSK-IMPACT and Caris Life Sciences and concordance with EBER ISH was evaluated in each cohort. Additional phenotypic classification was performed using clinicogenomic data from the Caris Precision Oncology Alliance. **Results:** A total of 91 pts who received ICI in the metastatic setting were included. Median age was 62 years (range 30-86) and 91% were male with pts from US (n = 15), Europe (n = 5), and Asia (n = 71). ECOG PS at the time of ICI was $\leq$1 in 97%. PD-L1 CPS score was $\geq$5 in 69%. Pts who received first-line chemotherapy + ICI (n = 42) achieved a 49% investigator-assessed ORR (CR/PR), median PFS (mPFS) 8.3 months (mo), and median OS (mOS) 38 mo compared with mOS 18 mo in pts receiving first-line chemotherapy alone (n = 35). Pts who received ICI-alone achieved a similar 49% ORR with 1L and later line mPFS 6 mo and 3.2 mo, respectively, which increase to 10.0 mo and 6.6 mo, when limiting to PD-L1 CPS $>$5. Univariate analysis for PFS among all pts demonstrated improved outcomes in those where PD-L1 CPS score was $\geq$5 (HR = 0.57, 95%CI:0.34,0.97). EBV detection by MSK-IMPACT and Caris achieved over 98% positive agreement and 99.9% negative agreement. Additional EBVaGC transcriptomic immune phenotyping data will be presented. **Conclusions:** This global EBVaGC experience demonstrated that EBVaGC can reliably be identified from NGS, negating the need for costly EBER ISH. Furthermore, pts with EBVaGC achieve a high ORR on ICI with or without concurrent chemotherapy. While 1L PFS was similar to non-EBVaGC, prolonged mOS was achieved, potentially reflecting frequent conversion surgeries and regional differences. Even among EBVaGC, immune heterogeneity exists, and PD-L1 CPS $>$5 identified pts who derived ICI benefit. Further research is needed to examine the patterns of disease progression in EBVaGC treated with ICI. Research Sponsor: None.

Second-line ASKB589 plus chemotherapy for advanced gastric or gastroesophageal cancers: Results from cohort 5 of a phase I/II study.

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Background: ASKB589 is a humanized monoclonal antibody with enhanced affinity for CLDN18.2 and increased ADCC activity. It has shown favorable safety profiles and promising antitumor effects in phase I/II clinical study (NCT04632108) involving first-line patient(pt)s with advanced gastric or gastroesophageal (G/GEJ) cancers. Here, we present the findings from cohort 5 that ASKB589 in combination with chemotherapy as second-line treatment for patients with advanced G/GEJ cancers. **Methods:** Cohort 5 from NCT04632108 is designed to evaluate the safety and preliminary efficacy of ASKB589 (at 2 doses: 6mg/kg or 10mg/kg Q3W) plus chemotherapy as second line treatment in pts with G/GEJ cancers. Eligible pts who had confirmed progressive disease during treatment with first line standard of therapy were enrolled. CLDN18.2 statuses were analyzed retrospectively using IHC DS-3 LDT assay. Primary endpoint was safety. Secondary endpoints included objective response rate (ORR), disease control rate (DCR), duration of response (DoR), progression free survival (PFS) assessed by investigator per RECIST v1.1 and overall Survival (OS). **Results:** As of December 20, 2024, 47 pts were enrolled in the 2L cohort and received 6mg/kg ASKB589 plus chemotherapy. Among them, 44 pts were treated with 6mg/kg ASKB589 plus paclitaxel, while 2 pts received 6mg/kg ASKB589 plus docetaxel, and 1 pt received 6mg/kg ASKB589 plus irinotecan. 17 (27%) pts had received immunotherapy previously.The confirmed ORR was 34.2% in 38 measurable and evaluable CLDN18.2 moderate to high GC/GEJ pts (CLDN18.2 moderate to high was defined as ≥40% of tumor cells with ≥2+ intensity by immunohistochemistry). 14 pts (36.8%) had stable disease, and the DCR was 71.1%. For the ASKB589 plus paclitaxel subgroup (n = 35, with evaluable response), the confirmed ORR was 31.1%, DCR was 71.4%. In the intention-to-treat analysis, the median PFS with 6mg/kg ASKB589 plus chemotherapy was 5.26 months (95%CI: 2.66, 7.06), and the median OS was 11.14 months (95%CI: 8.80, 18.20). In the ASKB589 plus paclitaxel subgroup, the median PFS was 4.63 months (95%CI: 2.04, 7.06) and median OS of 13.73 months (95%CI: 8.80, 18.20) respectively. Treatment related adverse events (TRAEs) occurred in all pts including 26 (55.3%) pts with grade ≥3 TRAEs. The most common grade ≥3 TRAEs (≥5%) were neutrophil count decreased (42.6%), white blood cell count decreased (17%), lymphocyte count decreased (8.5%), and hypoalbuminemia (8.5%). **Conclusions:** The results of cohort 5 from NCT04632108 have shown that ASKB589 plus chemotherapy, as 2L treatment in pts with advanced GC/GEJ cancers have promising antitumor activity and response durability, especially in the ASKB589 plus paclitaxel subgroups. Both treatment regimens are well tolerated. Further development of ASKB589 combination therapy for CLDN18.2-positive GC/GEJ pts 2nd line treatment is planned. Clinical trial information: NCT04632108. Research Sponsor: None.

Efficacy of venadaparib plus irinotecan in homologous recombination deficiency (HRD) gene mutations as 3+ line treatment in patients with metastatic gastric cancer (mGC).

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Background: Tumors with homologous recombination deficiency (HRD) have been suggested to be associated with a favorable response to poly (adenosine diphosphate [ADP]–ribose) polymerase (PARP) inhibitors. The aim of this analysis was to evaluate the association between the presence of HRD gene mutations and the efficacy of venadaparib, a novel PARP inhibitor, plus irinotecan in patients with metastatic gastric cancer (mGC) who had progressed after at least at least 2 lines of therapy. **Methods:** This was an exploratory analysis from a multinational, phase 1b/IIa trial of venadaparib plus irinotecan in patients with mGC (NCT04725994). Tumor response was evaluated according to RECIST v. 1.1. Genomic analysis was conducted using ctDNA (GuardantOMNI Gene Panel version 1.0, Redwood City, CA) on Day 1 pre-dose. Results of the exploratory genomic analysis, which includes pathogenic or deleterious mutations of following genes: *BRCA1/2*, *ATM*, *ATR*, *CHEK2*, *BARD1* were analyzed for association with efficacy outcomes. **Results:** As of Dec 2024, 43 patients enrolled and objective response (ORR), median progression-free survival (mPFS) and median overall survival (mOS) were 20.9%, 4.2 (2.9-9.6) and 8.1 (6.8-11.5) months. 14 (32.6%) out of the 43 patients had at least one HRD mutation (6 with *ATM*, 3 with *BRCA1*, 2 with *BRCA2*, 1 with *BARD1*, 1 with *CHEK2* and 1 with *ATR* mutations, respectively). For the 14 patients with HRD mutation and 29 patients with no HRD mutation, the ORR, mPFS (95% CI) and mOS (95% CI) were 35.7% vs. 13.8%, 5.6 (1.3-9.1) vs. 4.0 (2.7-5.4) months and 10.1 (6.8-12.0) vs. 8.0 (5.9-11.5) months respectively. For 11 patients with *ATM* or *BRCA1/2* mutation, mPFS (95% CI) and mOS (95% CI) were 8.4 (1.2-24.0) and 10.1 (6.8-34.4) months. At the maximum tolerable dose (MTD) level of venadaparib 20 mg/d on days 1 to 7 and irinotecan 100 mg/m^2 at day 1 of a 2-week cycle, six of 15 patients had HRD mutation, and mPFS (95% CI) and mOS (95% CI) were 4.1 (2.9-5.4) and 7.9 (5.9-11.5) months; these data are still maturing. **Conclusions:** Venadaparib in combination with irinotecan demonstrated promising efficacy in patients with mGC, particularly those with HRD gene mutations. Further development of this combination may warrant a biomarker-based approach. Clinical trial information: NCT04725994. Research Sponsor: Idience Co., Ltd.

Efficacy results in patients with homologous recombination deficiency mutation.

Patient #	Mutations in HRD-related Genes	Number of Prior Palliative Treatment	Best Overall Response (%)	Treatment Duration (months)	Overall Survival (months)
82001-2103	*BRCA2*	3	SD	25.1	33.9
82004-2101	*ATM*	2	PR	38.3	37.3
82002-2103	*ATR*	3	PD	1.4	8.0
82004-2103	*ATM*	3	PD	1.3	6.7
82004-2102	*BARD1*	2	CR	5.6	11.6
82005-2101	*ATM*	2	SD	3.1	11.8
82005-2103	*ATM*	2	PR	4.9	8.3
82003-2203	*BRCA2*	2	SD	9.4	11.5
82005-2202	*BRCA1*	2	SD	6.2	7.0
82003-2201	*CHEK2*	3	PR	3.1	3.1
82002-2203	*ATM*	2	SD	1.0	1.0
82004-2201	*ATM*	2	SD	0.5	0.5
82003-2205	*BRCA1*	2	SD	2.8	2.8
82001-2201	*BRCA1*	2	SD	5.3	7.8

Updated results of fruquintinib combined with PD-1 inhibitors and chemotherapy in the first-line treatment of HER2-negative advanced gastric or gastroesophageal junction adenocarcinoma (FDZL-FIX): A single-arm, open-label phase 2 study.

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Background: For unresectable locally advanced or metastatic HER2-negative gastric cancer (GC), the combination of chemotherapy with immunotherapy, specifically PD-1 inhibitors, has emerged as a new standard of care in first-line treatment of advanced GC, but the patients' outcomes remain poor. Fruquintinib (Fru) is a highly selective inhibitor of VEGFR1/2/3. We sought to explore the efficacy and safety of fruquintinib combined with PD-1 inhibitors and chemotherapy in the first-line treatment of HER2-negative advanced gastric or gastroesophageal junction adenocarcinoma. Here, we report the updated results. **Methods:** Eligible pts with HER2 negative locally advanced unresectable or metastatic gastric or gastrooesophageal junction adenocarcinoma, without any systemic anticancer treatment for advanced disease were included in the study. pts received 6 cycles of combined first line treatment with Fru (4mg p.o. qd, d1-14, q3w,) combined with PD-1 inhibitor (investigator's choice of sintilimab 200mg or nivolumab 360mg intravenously q3w) and chemotherapy (investigator's choice of XELOX or SOX) regimen. The following maintenance treatment was Fru combined with PD-1 inhibitor and S-1/capecitabine until disease progression or intolerable toxicity. The primary endpoint was progression-free survival (PFS). Secondary endpoints included objective response rate (ORR), overall survival (OS), disease control rate (DCR) and safety. **Results:** As of Jan 24, 2025, a total of 33 pts (22 male, 11 female) median age 62 (range: 35-77) were enrolled and received at least one dose of treatment. 30 patients had at least one tumor assessment post treatment, with an ORR of 80.0% (24/30; 95%CI 61.4-92.3) and DCR of 100%(30/30; 95%CI 88.4-100.0). In the intention to treatment (ITT) population, the median PFS was 9.43 months (95% CI 5.29-13.24) and the 9-month PFS rates was 57% (95%CI 40.0-83.0). The most common AEs of all grades were neutrophil count decreased (33.3%), palmar-plantar erythrodysesthesia syndrome (33.3%), and fatigue (30.3%). **Conclusions:** The combination of fruquintinib and chemotherapy with PD-1 blockade in the first-line treatment for unresectable locally advanced or metastatic HER2-negative GC had shown promising efficacy and acceptable safety profile. The results warrant further investigations in a large cohort. Clinical trial information: NCT06158919.
Research Sponsor: None.

Artificial intelligence-based prediction of claudin 18.2 expression and immune phenotype to guide treatment decisions in patients with gastric cancer.

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Background: With the increasing availability of immune checkpoint inhibitor (ICI)- and targeted agent-based treatments for gastric cancer, evaluating predictive biomarkers to guide first-line treatment has become increasingly complex. Claudin 18.2 (CLDN18.2) is a clinically relevant target for zolbetuximab-based chemotherapy, typically assessed by immunohistochemistry. However, limitations such as inadequate tumor specimens, high costs, and long turnaround times pose a practical challenge. **Methods:** An artificial intelligence (AI) model was developed to predict CLDN18.2 expression based on hematoxylin and eosin (H&E) slides from 459 patients with gastric cancer (derivation cohort). CLDN18.2 positivity was defined as moderate-to-strong expression in ≥75% of tumor cells. The AI model utilized a Vision Transformer-based architecture with a multiple-instance learning framework and was trained using five-fold cross-validation. Model performance was validated in two independent cohorts: an internal cohort of 381 patients treated with first-line ICI plus chemotherapy (ICI-Chemo) or chemotherapy alone (Chemo-only) and an external cohort of 100 patients from diverse ethnic backgrounds. Immune phenotypes (IPs) were assessed using an AI-powered whole slide image analyzer to further stratify patient outcomes. **Results:** The prevalence of CLDN18.2 positivity was 43.4% (derivation), 37.3% (internal validation), and 26.0% (external validation). The model achieved an AUROC of 0.753 in the derivation cohort, with sensitivity and specificity of 0.638 and 0.723, respectively. In the internal and external validation cohorts, AUROCs were 0.752 and 0.746, with similar sensitivity and specificity levels. Among the internal validation cohort, patients were stratified into subgroups based on predicted CLDN18.2 positivity and IP status. Among these, the subgroup predicted to be CLDN18.2-negative and inflamed IP demonstrated the most significant benefit from ICI-Chemo compared to the Chemo-only group. **Conclusions:** The AI model reliably predicted CLDN18.2 expression from H&E slides and exhibited reliable performance. The differential survival outcomes observed in subgroups stratified by AI-predicted CLDN18.2 expression and IP suggest its potential utility in guiding first-line treatment decisions for gastric cancer patients. Research Sponsor: Lunit.

Hazard ratio (HR) for progression-free survival (PFS) and overall survival (OS).

Groups	HR for PFS (95% CI)	HR for OS (95% CI)
CLND18.2-negative and inflamed IP	0.37 (0.17–0.78, p=0.009)	0.41 (0.19–0.88, p=0.021)
CLDN18.2-negative and non-inflamed IP	0.75 (0.54–1.05, p=0.095)	0.81 (0.59–1.13, p=0.224)
CLDN18.2-positive and inflamed IP	0.67 (0.40–1.12, p=0.128)	0.62 (0.37–1.04, p=0.073)
CLDN18.2-positive and non-inflamed IP	1.60 (0.74–3.46, p=0.229)	1.23 (0.59–2.58, p=0.579)

reference: Chemo-only.

Predictive value of homologous recombination-related gene mutations in survival outcomes of first-line nivolumab plus chemotherapy for gastric cancer.

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Background: Homologous recombination repair (HRR) gene mutations are associated with genomic instability; however, their clinical value in the context of immune checkpoint inhibitor (ICI)-based treatments in gastric cancer remains unclear. We investigated the efficacy of nivolumab plus chemotherapy according to the HRR mutation status in advanced gastric cancer patients. **Methods:** This single-center study included gastric cancer patients with available panel sequencing results who were treated with first-line nivolumab plus chemotherapy (n = 115) or chemotherapy alone (n = 172) between July 2021 and March 2024. Mutation status of 17 HRR genes (*BARD1*, *BLM*, *BRCA1*, *BRCA2*, *BRIP1*, *MRE11A*, *NBN*, *PALB2*, *PARP1*, *POLD1*, *RAD50*, *RAD51*, *RAD51C*, *RAD51D*, *RAD52*, *RAD54L*, and *XRCC2*) was assessed using targeted next-generation sequencing. Treatment outcomes were compared according to the presence of HRR mutations. **Results:** Among patients treated with nivolumab plus chemotherapy, 36.5% harbored HRR mutations. Compared to the no HRR mutation group, the HRR mutation group exhibited a higher objective response rate (92% vs. 63.2%, P = 0.010), longer progression-free survival (PFS) (median 12.8 vs. 6.5 months; hazard ratio [HR] 0.57, 95% confidence interval [CI] 0.36–0.91, P = 0.019) and overall survival (OS) (median not reached vs. 14.2 months; HR 0.40, 95% CI 0.23–0.71, P = 0.002). Among patients with HRR mutation, those treated with nivolumab plus chemotherapy showed favorable survival outcomes compared to those treated with chemotherapy alone (PFS: HR 0.44, 95% CI 0.27–0.71, P $<$ 0.001; OS: HR 0.45, 95% CI 0.25–0.80, P = 0.007), but this was not the case for patients without HRR mutation (PFS: HR 0.79, 95% CI 0.56–1.10, P = 0.156; OS: HR 0.90, 95% CI 0.63–1.28, P = 0.554). **Conclusions:** The presence of HRR mutations was associated with favorable survival outcomes in patients treated with nivolumab plus chemotherapy. Our findings suggest that HRR mutations may serve as a potential predictive biomarker for first-line ICI-based chemotherapy in gastric cancer. Research Sponsor: None.

Clinical outcomes of first-line immune checkpoint inhibitors with chemotherapy in advanced EBV-associated gastric cancer.

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Background: EBV-associated gastric cancer (EBVaGC) is a distinct subgroup of GC with high PD-L1/PD-L2 expression and immune cell infiltration. While several rationales support the potential efficacy of immune checkpoint inhibitors (ICIs) in EBVaGC, clinical evidence from large-scale trials is limited, and their effectiveness remains inconclusive. This retrospective study evaluated the clinical outcomes of palliative first-line chemotherapy with or without the addition of ICIs in patients with EBVaGC. **Methods:** We identified 217 patients diagnosed with EBVaGC via in situ hybridization and evaluated their baseline characteristics, including HER2 expression, MSI status, and PD-L1 expression. Among these, 83 patients with metastatic disease received palliative first-line treatment. Of the 77 HER2-negative patients, 23 were treated with ICIs (nivolumab or pembrolizumab) combined with cytotoxic chemotherapy (ICI+chemo), while 54 received chemotherapy alone. Survival outcomes and response rates were compared between ICI+chemo and chemotherapy-alone groups. **Results:** Among 217 EBVaGC patients, 8.5% were HER2-positive, 2.6% were MSI-High, and PD-L1 CPS $\geq$10 and $\geq$5 was observed in 59.1% and 84.1%, respectively. In HER2-negative EBVaGC patients, ICI+chemo showed significantly prolonged progression free survival (PFS) compared to chemotherapy alone (median: 9.28 vs. 6.07 months; HR = 0.48; p = 0.031). There was no significant difference in overall survival (OS) (median: 20.72 vs. 18.89 months; HR = 0.78; p = 0.508). The objective response rate (ORR) and disease control rate (DCR) were significantly higher in the ICI+chemo group than in the chemotherapy-alone group (ORR, 78.3% vs. 51.9%; OR = 3.29; p = 0.042; DCR, 100% vs. 79.6%; p = 0.028). In the ICI+chemo group, PD-L1 expression (cutoff: CPS 5 or 10) was not significantly associated with survival outcomes or response rates. For CPS $\geq$5, the median PFS was 7.84 months compared to 8.99 months in the CPS $<$ 5 group (p = 0.944), the median OS was 20.75 vs. 16.51 months (p = 0.131), and the ORR was 76.5% vs. 75.0%. For CPS $\geq$10, the median PFS was 13.9 months compared to 8.69 months in CPS $<$ 10 group (p = 0.580), the median OS was 24.95 months vs. 20.33 months (p = 0.061), and the ORR was 81.8% vs. 70.0%. **Conclusions:** To our knowledge, this study represents one of the largest cohorts including patients with EBVaGC who received first-line ICI+chemo. The addition of ICIs to chemotherapy showed clinical benefit, including survival and response rates, compared to chemotherapy alone in EBVaGC. Interestingly, the clinical benefit of ICI+chemo was observed in PD-L1 low group as well as PD-L1 high group. Our results highlight the clinical potential of ICI addition to chemotherapy in EBVaGC, and PD-L1 expression alone is insufficient as a predictive biomarker, warranting further exploration of alternative predictors for immunotherapy efficacy in this subgroup. Research Sponsor: None.

Phase II trial of transarterial chemoembolization followed by sintilimab (anti-PD-1), oxaliplatin, and S-1 combined with either trastuzumab (HER-2 positive) or apatinib (HER-2 negative) as first-line therapy for gastric cancer with liver metastases.

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Background: Liver metastases contribute to immunotherapeutic resistance and unfavorable outcomes. Transarterial chemoembolization (TACE) may alter the immune microenvironment and enhance immunotherapy efficacy. In this trial, we assessed the efficacy and safety of TACE followed by sintilimab (anti-PD-1), oxaliplatin and S-1 combined with either trastuzumab (HER-2 positive) or apatinib (HER-2 negative) in the treatment of gastric cancer with liver metastases (GCLM). Additionally, we explored gene mutations and the immune microenvironment between gastric cancer and its paired liver metastases. **Methods:** This single-center, single-arm, phase II trial enrolled 31 treatment-naive patients with GCLM. Patients received TACE for liver metastases, followed by sintilimab (200mg), oxaliplatin (130mg/m^2) and S-1 (40-60 mg bid for 14 days) every 3weeks combined with either trastuzumab (HER-2 positive, 8 mg/kg then 6 mg/kg, q3w) or apatinib (HER-2 negative, 250mg qd) until disease progression or intolerable toxicities. Tissue samples from gastric cancer and liver metastases were collected before treatment for DNA and RNA detection. The primary endpoints were PFS and ORR. The secondary endpoints were DCR, OS, and safety. **Results:** A total of 31 patients were enrolled, median 63 (41-76) years old, 27 male, 26 multiple liver metastases and all adenocarcinoma. Of them, 10 (32.3%) were HER2 IHC 3+, 7 (22.6%) HER2 IHC 2+/FISH+. Patients with PD-L1 CPS$\geq$5, $<$ 1 accounted for 19.4%, 51.6% respectively. With the median follow-up time of 396 days, the patients received a median of 6 treatment cycles. As of January 25, 2025, 27 patients were included in the efficacy and safety analyses. The ORR was 74.1%, with 5 CR, 15 PR, 3 SD, and 4 PD. DCR was 85.2%. The median PFS was 12 months, and the median OS was not reached. One- and two-year PFS rates were 51.6 and 27.1 %, respectively. One- and two-year OS rates were 89.1 and 74.0 %, respectively. Grade 3/4 treatment-related adverse events occurred in 18.5% of the patients, notably neutropenia, neurotoxicity and thyroid and liver dysfunctions. Forty-four unique mutated genes were identified in gastric cancer, which were involved in PI3K-Akt and drug resistance pathways. In its paired liver metastases, 59 specific mutated genes associated with *MMR* and cell cycle were identified. Liver metastases had more macrophages and CD8+ T cells, whereas NK and CD4+ memory resting cells were fewer than those in paired gastric cancer. **Conclusions:** TACE followed by sintilimab, oxaliplatin and S-1 combined with either trastuzumab or apatinib demonstrated promising efficacy and manageable safety as first-line therapy for GCLM. Gastric cancer and its paired liver metastases exhibited distinct gene mutations and immune microenvironment. Clinical trial information: ChiCTR2200057726. Research Sponsor: None.

Improving evidence-based treatment selection and patient-centered care in upper GI cancers: A Project ECHO initiative.

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Background: Accurate assessment of biomarkers (including HER2 and PD-L1) is integral to treatment selection in upper gastrointestinal (GI) cancers. However, challenges in integrating biomarker testing and targeted therapies are commonly reported in community settings. The Project Extension for Community Healthcare Outcomes (Project ECHO) model addresses this gap by connecting experts in tertiary care settings with rural healthcare teams. Through case-based teaching, the model builds the knowledge and skills needed to provide evidence-based, equitable care regardless of geographic location. **Methods:** In October 2024, 57 healthcare professionals (HCPs) from 2 US and 4 Canadian community oncology clinics participated in Project ECHO sessions. Led by an expert oncologist, each session featured interactive discussions of real-world anonymized case presentations to address key practice gaps in integrating biomarker-based therapies and coordinating multidisciplinary care for patients (pts) with upper GI cancers. Following each session, HCPs developed and implemented site-specific action plans to address gaps in care. Pre-activity and post-activity surveys measured the impact on knowledge, confidence, and competence and 90-day follow-up surveys will be collected to assess ongoing performance. **Results:** The top HCP-reported barriers to individualized care for pts with upper GI cancer included *keeping up with the latest efficacy and safety data* (44%), *selecting and sequencing treatments based on individual and disease factors* (40%), and *limited availability/cost of biomarker* testing (39%). Additionally, relatively few HCPs reported providing supportive care services for the majority of their patients, such as *palliative care referrals* (40%), *distress screening* (26%), *psychosocial support* (35%), and *end of life counseling* (19%). Following the Project ECHO sessions, HCPs demonstrated improved knowledge, competence, and confidence in biomarker testing and managing adverse events. Additionally, HCPs planned to *increase patient education about disease and treatment-related side effects* (65%), *improve team education on biomarker testing and treatment selection* (61%), *establish standardized biomarker testing protocols (35%),* and *increase supportive care referrals (22%).* Team action plans included implementing routine testing protocols, establishing a network of specialists to coordinate care, and increasing education on the use of immunotherapy. **Conclusions:** Project ECHO-based education improved HCP capacity to integrate biomarker-directed therapies and coordinate multidisciplinary care for patients with upper GI cancers. Full findings will detail long-term impacts on practice and inform future community-based ECHO initiatives. Research Sponsor: Bristol Myers Squibb.

Comparison of postoperative adjuvant therapy and surgery alone in pathological N1-2 esophageal squamous cell carcinoma: A prospective multi-center randomized controlled trial.

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Background: Due to the lack of prospective randomized controlled clinical studies, current guidelines do not recommend postoperative adjuvant therapy, but rather observational follow-up regardless of any stage. The aim of this study was to evaluate the effect of postoperative adjuvant chemoradiotherapy and adjuvant chemotherapy on pathologic lymph node-positive (pN1-2) esophageal squamous cell carcinoma (ESCC). **Methods:** Patients with pathologically confirmed pN1-2 ESCC were randomly assigned to three groups: surgery alone (SA), postoperative chemotherapy (POCT), or postoperative chemoradiotherapy (POCRT). The POCT regimen included 2 to 4 cycles of docetaxel and cisplatin (75 mg/m^2), while the POCRT regimen comprised 28 fractions of 5040Gy radiotherapy combined with docetaxel and cisplatin. Overall survival (OS) was the primary endpoint. Recruitment was terminated early due to the significant benefit observed in the adjuvant therapy group and difficulties in enrollment. **Results:** A total of 145 patients were enrolled (SA: n = 50, POCT: n = 48, POCRT: n = 47), with a median follow-up of 55 months. The overall survival rates at 3 and 5 years were 76.1% and 56.2% in the POCRT group, compared with 56.6% and 43.4% in the POCT group and 49.1% and 25.0% in the SA group, respectively. The POCRT group showed significantly improved OS and DFS compared to the SA group (OS, P = 0.003; DFS, P = 0.003). The incidence of grade 3 or higher adverse events was 39.6% in the POCT group and 44.7% in the POCRT group (P = 0.615). **Conclusions:** For patients with pN1-2 ESCC, postoperative therapy, especially postoperative chemoradiotherapy, significantly improved the prognosis of patients compared with surgery alone. Clinical trial information: NCT04009265. Research Sponsor: Fujian Minimally Invasive Medical Center (Thoracic Surgery), China; Key Laboratory of Cardio-Thoracic Surgery(Fujian Medical University), Fujian Province University; Fujian Institute of Cardio-thoracic Surgery, China.

Combined PD-L1 expression and PD-1+ CD8 T cells to predict immunotherapy outcomes in esophageal squamous cell carcinoma.

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Background: Esophageal squamous cell carcinoma (ESCC), the predominant subtype of esophageal cancer in Asia, remains a challenging disease with poor prognosis due to frequent late-stage diagnoses. Immune checkpoint inhibitors (ICIs), particularly those targeting the PD-1/PD-L1 axis, have revolutionized cancer treatment but benefit only a subset of patients. The identification of robust predictive biomarkers is critical to enhance patient selection and optimize immunotherapy outcomes. In this study, we leveraged multiplex immunofluorescence to comprehensively evaluate the roles of PD-L1 and PD-1 expression, immune cell subsets, and clinical factors in predicting immunotherapy efficacy in ESCC. **Methods:** We analyzed baseline tumor samples from 147 ESCC patients treated with first-line ICIs using multiplex immunofluorescence to assess the expression of PD-1, PD-L1, CD4, CD8, CD20, and CD68. Patients were stratified by biomarker expression levels, with cut-off values determined through ROC curve analysis to calculate AUC. Survival outcomes were analyzed, and multivariate Cox regression identified independent predictors of progression-free survival (PFS) and overall survival (OS). **Results:** PD-L1 expression (HR 0.266, 95%CI 0.087-0.816, p = 0.021) and PD-1+CD8+ T cells (HR 2.694, 95%CI 1.162-6.246, p = 0.021) emerged as independent predictors of PFS. High PD-L1 expression was associated with superior outcomes (mPFS: 7.6 vs. 5.5 months), while elevated PD-1+CD8+ T cell infiltration correlated with poorer outcomes (mPFS: 6.0 vs. 7.2 months). Patients with a combination of high PD-L1 expression and low PD-1+CD8+ T cells demonstrated the best prognosis, with a median PFS of 8.5 months, whereas those with low PD-L1 expression and high PD-1+CD8+ T cells had the worst prognosis, with a mPFS of 3.5 months. Clinical stage (HR 1.570, 95%CI 1.059-2.327, p = 0.025), BMI (HR 0.935, 95%CI 0.883-0.990, p = 0.015), and CD8+ T cell density (HR 0.896, 95%CI 0.824-0.975, p = 0.011) were identified as independent predictors of OS. **Conclusions:** Our findings uncover the dual importance of PD-L1 expression and PD-1+CD8+ T cell infiltration as critical biomarkers for predicting PFS in ESCC patients undergoing ICIs. Moreover, clinical factors such as BMI, tumor stage, and intratumoral CD8+ T cell density significantly impact OS. Research Sponsor: None.

Temporal and spatial expression of CLDN18.2 in gastric cancer and gastro-esophageal junction cancer.

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Background: Recent studies have demonstrated the promising efficacy of CLDN18.2-targeted therapy in patients with gastric cancer (GC) or gastroesophageal junction cancer (GEJC) who are positive for CLDN18.2. This study aims to investigate the temporal and spatial consistency of CLDN18.2 expression in GC and to provide a comprehensive overview of its expression patterns. **Methods:** The expression of CLDN18.2 in primary GC tumors (biopsy/surgical) and corresponding peritoneal metastases (PM) was evaluated by quantifying cell membrane staining intensity with a validated semi-quantitative assay. CLDN18.2 positivity was defined when tumor cells with staining intensity (2+) and (3+) summed up to $\geq$ 75% of all. The Kappa test evaluated CLDN18.2 expression consistency across sample types, and the McNemar test compared its positive rates in paired samples. **Results:** Between February 2023 and April 2024, 536 patients were enrolled at the Gastric Cancer Center of West China Hospital, Sichuan University. The cohort comprised 399 in-situ biopsy samples, 240 radical gastrectomy samples, and 27 peritoneal biopsy samples. Among them, 109 patients had biopsy and surgical specimens, and 26 underwent preoperative neoadjuvant therapy. Among 399 biopsy specimens, 131 (32.8%) had positive CLDN18.2. In 240 surgical specimens, 167 (27.9%) were positive. In 27 peritoneal nodule specimens, 10 (37.0%) were positive. No significant differences were found (χ^2 = 2.128, P = 0.345). Among 109 patients with paired biopsy and postoperative pathology, CLDN18.2 expression concordance was 80.7% (88/109, Kappa = 0.562). In 27 peritoneal metastasis patients, it was 77.8% (21/27, Kappa = 0.503). For 26 chemo-resected patients, the pre-and post-chemo positive concordance was 80.8% (21/26, Kappa = 0.524). All showed moderate consistency. CLDN18.2 expression significantly correlated with several factors, including gender (P = 0.002), histological subtype (P = 0.003), tumor location (P = 0.007), histological classification (P = 0.035), and EBV status (P = 0.006). Higher rates were in females, signet-ring cell carcinoma, non-GEJ tumors, poorly differentiated tumors, and EBV-positive patients. **Conclusions:** CLDN18.2 is widely present in both primary gastric cancer and peritoneal metastatic lesions. Expression consistency exists moderately between biopsy and surgical specimens, and primary and metastatic tissues. Consistency stays strong pre- and post-neoadjuvant therapy. Its expression links to clinical and molecular traits. This study comprehensively analyzed it, providing a better basis for CLDN18.2-targeted patient selection. Research Sponsor: None.

Safety and efficacy of endoscopic treatment with mucosal resection, radiofrequency ablation, and cryotherapy in the curative treatment of early esophageal squamous cell cancer and dysplasia.

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Background: Endoscopic esophageal treatment (EET), by radiofrequency ablation (RFA), cryoablation (Cryo), and endoscopic mucosal resection (EMR) has not been extensively studied in early esophageal squamous cell carcinoma (SCC). Aim: To assess the safety and success of EET in curative treatment of early esophageal SCC: (T1a, T1b, T2) and squamous cell dysplasia (SCD). **Methods:** We retrospectively reviewed records of patients with SCC (T1a, T1b, T2) and SCD treated with EET from January 2010 to August 2024. All patients had at least one follow-up endoscopic biopsy after treatment. **Results:** 62 patients met the eligibility criteria. Table. 46 patients (74%) had T1a (n=36.5%) or T1b (n=10.1%) SCC. T2 patients (21%) received ETT for local recurrence after chemoradiation. The most frequent ETT was EMR + RFA, n= 26 (41.9%) and RFA, n=20 (32%). In the first biopsy after treatment, 46 of the 62 patients (74.1%) had no residual cancer. This number increased after further ETT. 2 years after treatment only 4 patients had persistent cancer. BMI is significantly associated with survival status. No patient had disease progression that required surgery. Strictures formed in 15 patients (24%) post- ETT. **Conclusions:** ETT provides curative treatment of early SSC in up to 94% of patients. Research Sponsor: None.

Association between cancer persistence at first post-biopsy with various demographic and clinical variables.

Patient Characteristics		Total N=62	P-value
Sex (%)			
	Male	28 (45.16%)	0.49
	Female	34 (54.84%)	
Race (%)			
	White / Caucasian	52 (83.87%)	0.716
	Hispanic	2 (3.23%)	
	Black	2 (3.23%)	
	Asian	4 (6.45%)	
BMI, median (range)	N = 62	24.02 (15, 44.5)	0.045
Smoking Status (%)			
	No	25 (40.32%)	0.182
	Yes	37 (59.68%)	
Alcohol Drinking (%)			
	No	22 (35.48%)	>0.99
	Yes	40 (64.52%)	
Squamous Dysplasia (%)			
	none	59 (95.16%)	>0.99
	Low	1 (1.61%)	
	High	2 (3.23%)	
Squamous tumor staging (%)			
	none	3 (4.84%)	0.174
	T1a	36 (58.06%)	
	T1b	10 (16.13%)	
	≥T2	13 (20.97%)	
Squamous Tumor Differentiation (%)			
	Well	5 (8.2%)	0.707
	Moderate	47 (77.05%)	
	Poor	9 (14.75%)	
Lymphovascular Invasion (%)			
	No	57 (91.94%)	>0.99
	Yes	5 (8.06%)	

1b) Patient survival status - Immediate Post-Treatment Pathology Finding

Patient Characteristics		Total N=62
First biopsy post-treatment finding (%)		
	No dysplasia or cancer	37 (59.68%)
	Persistent cancer (Failure of t/t)	16 (25.81%)
	Persistent Dysplasia	9 (14.52%)

1c) Patient survival status ≥2 years post-treatment, excluding patients with no data or recurrent cancer/ dysplasia

Patient Characteristics		Total N=21
Biopsy finding (%)		
	No dysplasia or cancer	15 (71.43%)
	Persistent cancer (Failure of t/t)	4 (19.05%)
	Persistent Dysplasia	2 (9.52%)

Safety and efficacy of camrelizumab combined with radiotherapy as neoadjuvant therapy for locally advanced esophageal squamous cell carcinoma: A prospective single-arm phase II clinical trial.

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Background: Neoadjuvant chemoradiotherapy followed by esophagectomy is the standard of care for locally advanced esophageal squamous cell carcinoma (ESCC). However, approximately 30% of patients still develop distant metastases and have a high incidence of treatment-related adverse events. Immunotherapy, as a new modality for anti-cancer treatment, has shown promising clinical benefits for patients with ESCC. The synergistic effects of immunotherapy and radiotherapy make their combination promising as neoadjuvant treatment for locally advanced ESCC. **Methods:** All participants who meet the inclusion criteria will be enrolled after signing the informed consent form. Patients with thoracic segment esophageal cancer with clinical stage T2-3 N0 M0 or T2-3 N+ M0 will be included. They will be treated with radical surgery within 4–8 weeks after the completion of two cycles of neoadjuvant radiotherapy in combination with camrelizumab according to the study schedule. The primary endpoint is the major pathological remission rate of all per-protocol patients. The secondary endpoints are the R0 resection rate, pathological complete remission rate, and adverse events. The interim analysis will be conducted after half of the planned number of patients have been enrolled. The trials will be terminated when more than two treatment-related deaths occur or fewer than five patients have major pathological remission. **Results:** A total of 25 patients were enrolled, 3 patients did not undergo surgery, of which 1 had imaging CR after neoadjuvant therapy and refused surgical treatment; 1 progressed during neoadjuvant therapy, and the other had immune pneumonitis and renal insufficiency during neoadjuvant therapy. The final results of the study noted that of the 22 patients who underwent surgery. Twelve of 22 (54.5%) patients had a pathologic response, all consisting of an MPR with ≤10% RVT, including 8 of 22 (36.4%) pathologic complete responses. **Conclusions:** The NRIT regimen is safe and feasible for patients with ESCC. Clinical trial information: NCT05176002. Research Sponsor: Key Laboratory of Cardio-Thoracic Surgery (Fujian Medical University), Fujian Province University; Fujian Minimally Invasive Medical Center (Thoracic Surgery), China; Fujian Institute of Cardio-thoracic Surgery, China.

A real-world, propensity-matched analysis of second-line (2L) FOLFIRI-Ram versus Ram-Pac in advanced upper gastrointestinal cancers.

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Background: Given historically poor outcomes for advanced upper gastrointestinal (UGI) cancers, there is an urgent need for effective 2L treatments. Since the phase III RAINBOW trial, combination ramucirumab and paclitaxel (Ram-Pac) has filled this role; however, this regimen is plagued by dose-limiting toxicities, specifically neuropathy. The phase II RAMIRIS trial demonstrated the efficacy and tolerability of FOLFIRI-Ram as an alternative 2L, even if it did not improve survival over Ram-Pac. Real-world data to support its use, however, are lacking. **Methods:** The nationwide Flatiron Health electronic health record-derived de-identified database, which includes treatment data from around 280 cancer clinics across the United States, was queried for patients treated for unresectable or metastatic UGI cancers with 2L Ram-Pac or FOLFIRI-Ram from January 2011-June 2024. Demographics and lab values at time of treatment were extracted. Study cohorts were derived using a greedy match based on a logit model to predict propensity scores from key clinical and laboratory characteristics; patients were matched 1:6 (FOLFIRI-Ram:Ram-Pac) given expected imbalances in sample size. The endpoints of interest were overall survival (OS) and real-world time to treatment discontinuation (rwTTD), determined via Kaplan-Meier method, log-rank test, and Cox proportional hazards model. A hybrid approach was used to construct a multivariate Cox model. **Results:** Of 15,908 UGI cancer patients identified, 631 received 2L Ram-Pac and 40 received 2L FOLFIRI-Ram. After matching, 40 FOLFIRI-Ram and 240 Ram-Pac patients were included. Median OS from initiation of 2L therapy was 9.7 months with FOLFIRI-Ram (95% CI 6.9-12.3) and 7.7 months with Ram-Pac (95% CI 6.2-8.8), with a hazard ratio (HR) for death of 0.74 with FOLFIRI-Ram versus Ram-Pac (95% CI 0.50-1.11, p = 0.14). Similar results were seen in the multivariate model (HR 0.72, 95% CI 0.49-1.08, p = 0.114) after adjustment for albumin, neutrophil:lymphocyte ratio, and alkaline phosphatase. The median rwTTD with FOLFIRI-Ram was 5.2 months (95% CI 4.1-6.2), compared to 3.7 months with Ram-Pac (95% CI 3.2-4.3). The HR for treatment discontinuation was 0.70 with FOLFIRI-Ram versus Ram-Pac (95% CI 0.48-1.00, p = 0.048). The reduced hazard for treatment discontinuation with FOLFIRI-Ram persisted in the multivariate model (HR 0.67, 95% CI 0.46-0.97, p = 0.033) after adjustment for ECOG status, history of prior surgery, PDL1, albumin, and neutrophil:lymphocyte ratio. **Conclusions:** In a real-world propensity-score matched analysis, no survival difference was noted with the combination of FOLFIRI-Ram compared to Ram-Pac, however FOLFIRI-Ram was associated with a significantly longer rwTTD. Altogether, these data suggest FOLFIRI-Ram is a viable and tolerable alternative for 2L treatment of UGI cancers. Research Sponsor: None.

4059 Poster Session

Disitamab vedotin (RC48), tislelizumab, and S-1 as first-line therapy for HER2-overexpressing advanced gastric or gastroesophageal junction adenocarcinoma (GC/GEJC): Updated results from the RCTS trial.

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Background: Anti-PD1 antibody has significantly improved survival in patients with HER2-overexpressing and PD-L1 combined positive score (CPS) ≥1 GC/GEJC when added to trastuzumab and chemotherapy. Recent trials revealed that HER2-targeted antibody-drug conjugates, including RC48 and Trastuzumab Deruxtecan, combined with anti-PD1 antibody, have also shown promising efficacy in this population. This study reports updated survival results of RC48 combined with tislelizumab and the oral fluoropyrimidine S-1 as first-line therapy for patients with HER2-overexpressing GC/GEJC. **Methods:** This single-arm, multicenter clinical trial enrolled patients with unresectable or metastatic HER2-overexpressing (IHC 3+ or 2+, regardless of FISH status) first-line GC/GEJC. Patients received RC48 (2.5 mg/kg), tislelizumab (200 mg), and S-1 (40-60 mg BID for 14 days) every 3 weeks until disease progression (PD) or intolerable toxicity. The primary endpoint was objective response rate (ORR). Secondary endpoints were progression-free survival (PFS), overall survival (OS) and safety. **Results:** 57 patients from 9 centers were enrolled, 71.9% HER2 IHC 3+, 17.5% IHC 2+/FISH+, and 10.5% IHC 2+/FISH-. 14.9% and 36.2% had CPS≥5 and ≥1, respectively. Median follow-up was 11.8 months. In the intent-to-treat population, the confirmed ORR (cORR) was 89.4% (51/57, 95% CI: 78.5-96.0%), the median PFS (mPFS) was 12.7 months (95% CI: 10.9-NA), and the 18-month OS rate (18m-OSr) was 72.7% (95% CI: 60.0-88.5%). In the per-protocol set (excluding patients with no PD at the first assessment but refused a second evaluation), the cORR was 92.7% (51/55, 95% CI: 82.4-98.0%), the mPFS was 13.2 months (95% CI: 10.9-NA), and the 18m-OSr was 76.3% (95% CI: 63.0-91.7%). In the HER2-positive and -negative subgroups, the ORRs were 92.1% (95% CI: 81.1-97.8%) and 66.7% (95% CI: 22.3-95.7%), the mPFS was 12.6 months (95% CI: 11.0-NA) and 7.7 months (95% CI: 7.1-NA), and the 18m-OSr was 74.7% (95% CI: 61.3-91.1%) and 62.5% (95% CI: 32.0-100%), respectively. In the CPS ≥1 and CPS < 1 subgroups, ORRs were 92.3% (95% CI: 74.9-99.1%) and 87.1% (95% CI: 70.2-96.4%), the mPFS was 16.8 months (95% CI: 11.3-NA) and 11.4 months (95% CI: 8.5-NA), and the 18m-OSr was 80.4% (95% CI: 62.1-100%) and 67.4% (95% CI: 50.7-89.5%), respectively. The grade 3-4 treatment-related adverse events (AEs) was 63.2%. The most common AEs were neutropenia, fatigue, and leukopenia. An exploratory study with longitudinal sequencing of circulating tumor DNA is ongoing. **Conclusions:** The combination of RC48, tislelizumab and S-1 as a first-line therapy shows encouraging response rates and survival benefits in HER2-overexpressing GC/GEJC, especially in HER2-positive or CPS ≥1 patients, supporting further evaluation in randomized controlled trials. Clinical trial information: NCT05586061. Research Sponsor: None.

Health-related quality of life (HRQoL) with paclitaxel plus ramucirumab (PTX-RAM) switch maintenance versus continuation of first-line fluoropyrimidine and oxaliplatin (FOX) chemotherapy (ChT) in patients (pts) with advanced HER2-negative gastric or gastroesophageal junction (G/GEJ) cancer: A secondary endpoint of the ARMANI phase 3 randomized trial.

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Background: PTX-RAM switch maintenance significantly improved PFS (HR 0.61, 95%CI 0.48–0.79; p = 0.0002) and OS (HR 0.75, 95%CI 0.58–0.96; p = 0.025) versus continuation of FOX first-line ChT in the ARMANI trial, with a higher incidence of grade ≥3 treatment-related adverse events and an increased number of hospital visits. Here we present HRQoL results. **Methods:** ARMANI was an Italian multicenter, open-label, randomized, phase 3 trial enrolling pts with HER2-negative G/GEJ cancer who had disease control after a 3-month FOX induction ChT, and randomized to switch maintenance with PTX-RAM or the continuation of FOX. European Organisation for Research and Treatment of Cancer (EORTC) QLQC30, QLQOG25 and EuroQol EQ5D were assessed at randomization and every 8 weeks until progression. HRQoL changes over time were described by: (i) mean changes from baseline at each time point, (ii) distribution of improved/stable/worse at 8 weeks and (iii) time to QoL deterioration (TTD), defined as the time from randomization to a worsening ≥ 10 points of global QoL in EORTC QLQC30. Mean changes were compared by a linear regression model, with baseline values as covariates. Proportion of improved/stable/worse was compared by Chi square test. Kaplan-Meier and Cox proportional hazards model were used for TTD estimation. **Results:** Of the 280 pts randomized, 198 (71%; 109/144 with PTX-RAM and 89/136 with FOX) and 133 (48%; 81/144 and 52/136) completed baseline and 8-weeks assessment of EORTC and EQ5D, respectively. Mean baseline scores of global HRQoL were 66.90 (standard deviation [SD] 20.71) with PTX-RAM and 70.97 (SD 19.39) with FOX. Global QoL at 8-weeks assessment was better with PTX-RAM versus FOX both in terms of mean changes from baseline (+2.17 vs -8.51, delta 10.68, p = 0.015) and in terms of proportion of improved/stable/worse (improved 24.7% vs 4.2%, stable 56.2% vs 64.6%, worse 19.2% vs 31.3%, p = 0.009). TTD was significantly longer for PTX-RAM versus FOX (median TTD 7.6 vs 3.8 months, HR 0.52, 95%CI 0.33-0.82; p = 0.005). Mean changes from baseline after 8 weeks for functional scales and symptoms of QLQC30 and QLQOG25 showed significant improvement for PTX-RAM vs FOX for role functioning (p = 0.006), nausea/vomiting (p = 0.002), pain (p = 0.016), appetite loss (p = 0.03) and dysphagia (p = 0.028); hair loss was worse with PTX-RAM (p = 0.024). VAS score from EQ5D was not significantly different between the two treatments for all the assessments. **Conclusions:** In pts with HER2-negative advanced G/GEJ cancer, PTX-RAM switch maintenance, beyond a significant benefit in PFS and OS, showed significant benefit in terms of HRQoL, reducing symptoms and delaying global QoL deterioration. Clinical trial information: NCT02934464. Research Sponsor: None.

Feasibility of circulating tumor DNA-based minimal residual disease (ctDNA-MRD)-guided adjuvant chemotherapy in patients with stage II-III gastric cancer (GC): An adaptive trial (MRD-GATE).

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Background: Although adjuvant chemotherapy (ACT) is the standard treatment for stage II-III GC, this strategy lacks precision treatment options, and many patients cannot tolerate the adverse events (AEs) of ACT. ctDNA-MRD detection has been shown to predict recurrence risk. The aim of this study (NCT06157216) was to evaluate the feasibility of MRD-guided treatment in these patients. **Methods:** Patients with stage II-III GC who underwent R0 resection and D2 gastrectomy were enrolled. Tumor-informed ctDNA-MRD testing was performed at baseline (28 days after surgery) and subsequently at 3, 6, 9, 12, 18, 24, 30, and 36 months after surgery. ACT was tailored according to MRD status: baseline MRD-negative (MRD (-)) patients received de-escalated therapy (observation for stage II and S-1 monotherapy for stage III) and switched to combined ACT (SOX, S-1 plus oxaliplatin, or XELOX, capecitabine plus oxaliplatin) if MRD became positive, while baseline MRD-positive (MRD (+)) patients underwent combined ACT. The primary endpoint was 3-year disease-free survival rate (yDFSr). Secondary endpoints included the treatment de-escalation rate, DFS by MRD status, cumulative recurrence risk (CRR), 3-year overall survival rate (yOSr) and safety. **Results:** 65 patients were enrolled, with a median age of 60 years (range: 34-83), and 83.1% (54/65) were male, 31 patients had stage II and 34 patients had stage III GC. At baseline, 21.5% patients (14/65) were MRD(+) and received combination ACT. Among the 51 baseline MRD(-) patients, 45 received de-escalated therapy at onset (9 received combination ACT after MRD conversion) and 6 received combination ACT. The median follow-up time was 13.3 (range: 9.3-15.7) months. In the intention-to-treat population, the overall 1-yDFSr was 86.2% (90% CI: 79.4-93.5%), the 1-yOSr was 96.9% (90% CI: 93.5-100%) and the CRR was 13.8% (95% CI: 6.5-24.7%). The treatment de-escalation rate was 69.2% (45/65, 95% CI: 56.6-80.1%). Grade 3-4 AEs occurred in 24.6% (95% CI: 14.8%-36.9%) of patients. Baseline MRD (+) patients had a shorter DFS compared to MRD (-) ones (1-yDFSr: 57.1% vs. 94.1%, HR = 9.66, 95% CI: 2.40-38.81, log-rank $P < 0.0001$). Patients with sustained MRD (-) had the best DFS (1-yDFSr: 100%), while those with sustained MRD (+) had the shortest DFS. Patients with MRD conversion from positive to negative or from negative to positive had intermediate DFS (1-yDFSrs: 72.7% and 70.0%, respectively). In 9 patients with recurrence, ctDNA-MRD positivity identified recurrence a median of 3.4 months earlier than radiology. **Conclusions:** MRD-guided ACT for stage II-III GC significantly reduced the ACT rate, and increased the de-escalated CT rate, resulting in good disease-free survival and fewer side effects. The results of this MRD-guided precision of ACT deserve to be confirmed by large randomized clinical trials. Clinical trial information: NCT05585580. Research Sponsor: None.

Development and validation of the gastric risk immuno-progression score (GRIPS) in advanced gastric and gastroesophageal junction adenocarcinoma treated with first-line chemotherapy plus nivolumab: Results from the ORACLE study.

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Background: The addition of nivolumab to chemotherapy is approved for advanced gastric and gastroesophageal junction (GEJ) adenocarcinoma with PD-L1 CPS ≥5. Identifying predictive tools for disease progression in this setting remains a clinical need. This study introduces the Gastric Risk Immuno-Progression Score (GRIPS), a novel score derived from variables associated with progression-free survival (PFS) in a real-world cohort. **Methods:** We conducted a multicenter retrospective study on 90 patients with gastric/GEJ adenocarcinoma treated with first-line chemotherapy plus nivolumab between 2022 and 2024. The GRIPScore was constructed using five dichotomous variables associated with unfavorable PFS in univariate analysis: Neutrophil-to-Lymphocyte Ratio (NLR > 2.68), ECOG Performance Status (≥2), Smoking status (never smoker), CA19.9 at diagnosis (UNL) and primary tumor resection (no resection). Each variable was scored as 1 (prognostically negative) or 0 (prognostically positive), and a total score (0–5) was calculated. Patients were categorized into low-risk (GRIPS 0–2) and high-risk (GRIPS 3–5) groups. PFS and OS were analyzed using Kaplan-Meier methods. Hazard Ratios (HRs) were calculated, and the discriminatory ability of the GRIPS was evaluated using Harrell's C-index. **Results:** The median PFS for the entire cohort was 11.55 months (95% CI: 7.60–13.26). Stratifying patients by GRIPS revealed a marked difference in outcomes between the low-risk and high-risk groups. Low-risk patients (GRIPS 0–2) had a median PFS of 13.16 months (95% CI: 9.01–18.91), while high-risk patients (GRIPS 3–5) had 4.11 months (95% CI: 2.37–11.77). This difference was significant (log-rank test, p = 0.0023; HR: 3.55, 95% CI: 1.58–8.02). Similarly, low-risk patients had a median OS of 21.25 months (95% CI: 13.77–21.25) compared to 11.90 months (95% CI: 4.03–16.10) for high-risk patients (log-rank test, p = 0.0313; HR: 2.73, 95% CI: 1.09–6.81). Harrell's C-index for PFS was 0.648 (95% CI: 0.552–0.743), indicating moderate discriminatory ability. **Conclusions:** The GRIPS effectively stratifies patients with advanced gastric and gastroesophageal junction adenocarcinoma treated with a combination of chemotherapy + nivolumab into distinct risk groups for PFS and OS. High-risk patients experience significantly shorter survival, highlighting the potential clinical utility of GRIPS for personalized treatment strategies. Further prospective validation is warranted to refine its application in clinical practice. Research Sponsor: None.

GRIPScore	N° of patients (%)	mOS (m)	mPFS (m)
Low-risk (0-2)	51 (45.9)	21.25 (95% CI: 13.77–21.25)	13.16 (95% CI: 9.01–18.91)
High-risk (3-5)	21 (18.9)	11.90 (95% CI: 4.03–16.10)	4.11 (95% CI: 2.37–11.77)
Not evaluable	18 (16.2)		

4063 Poster Session

Multicenter phase I/II study of abemaciclib and ramucirumab in metastatic gastroesophageal adenocarcinoma (GEA): CDK4/6 and cyclin D1 alterations as a predictor of response and survival.

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Background: CDK4/6 and Cyclin D1 are highly expressed in GEA cancers, suggesting that CDK4/6 inhibition may be a promising strategy. *In vitro and in vivo* studies have shown that abemaciclib (A) demonstrates potent antitumor efficacy in GEA by directly inhibiting this pathway. Currently, ramucirumab (RAM) ± paclitaxel is an approved 2nd line treatment for metastatic GEA cancers. **Methods:** This multicenter, open-label, phase I/II study investigated the safety and efficacy of A combined with RAM in pretreated advanced GEA (2nd or 3rd line). The primary objective was to describe the safety profile of A (150mg po bid) and RAM (8mg/kg iv every 2 weeks) using CTCAE version 4.03. Secondary objectives included assessing the objective response rate (ORR), disease control rate (DCR), median progression-free survival (mPFS), and median overall survival (mOS). Correlative studies to evaluate alterations in CDK4/6 and Cyclin D1 as determined by next generation sequencing as predictive biomarkers of efficacy were performed. **Results:** From July 2021 to December 2024, 20/30 patients were enrolled. The study was terminated prematurely due to slow accrual. The median age was 61.5 years (Range: 30.0, 80.0) and most patients were male (18/20). Seven patients (35%) were HER-2 positive, 11/18 patients (61.1%) were PDL1 CPS >1 and 15 patients (75%) had cancer localized in the E. Baseline ECOG performance status was 0 in 8 patients (40%) and 55% of patients had received prior immunotherapy with 1st line chemotherapy. A combined with RAM was generally well-tolerated without unexpected toxicities. The most common treatment-related adverse events (AEs) were anemia (10%), hypertension (10%), and dysphagia (10%). Treatment-related AEs $\geq$ grade 3 occurred in 50% of the patients. Median PFS and mOS were 2.7 months (95% CI: 1.5 - 14.5) and not reached (NR) (95% CI: 3.4 - NR), respectively. ORR was 10% (2/20) and DCR was 40% (8/20). In evaluable patients, 64.7% (11/17) patients with baseline tissue CDK4/6 pathway alterations trended towards longer mPFS (3.4 vs. 1.3 months; HR:1.1) and mOS (NR vs. 5.2 months; HR: 1.4) compared to patients without alterations ($p > 0.05$). Notably, one study patient with a CDK6 amplification had a partial response of 64% and has been on treatment for $>$ 24 months. **Conclusions:** A plus RAM demonstrated promising antitumor activity in previously treated E/GEJ adenocarcinomas in the 2nd and 3rd line metastatic setting with manageable toxicities. Alterations in the CDK4/6 and Cyclin D1 pathways appear to enrich for efficacy and may be predictive but need future validation. In-depth molecular studies investigating changes in the expression of selected serum/tissue genomic markers of response for the cytostatic regimen will be presented at the meeting. Clinical trial information: NCT04921904. Research Sponsor: None.

Sequential chemo-immunotherapy as a novel bridging strategy for non-complete responders after neoadjuvant chemoradiotherapy in esophageal cancer: First prospective phase 2 trial challenging the immediate-surgery paradigm.

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Background: Locally advanced esophageal squamous cell carcinoma (LA-ESCC) patients with non-clinical complete response (non-CCR) after neoadjuvant chemoradiotherapy (NCRT) face >50% recurrence risk with direct surgery (DS), yet no standardized bridging strategy exists. This first study evaluates the efficacy and safety of sequential chemo-immunotherapy (SCI) as a bridge to surgery in this population. **Methods:** In this phase 2 cohort study (NCT05189730), 169 LA-ESCC pts who underwent NCRT were prospectively enrolled from June 2021 to January 2025. The NCRT regimen included paclitaxel and carboplatin every 3 weeks for two cycles. Concurrent radiotherapy (40–41.4 Gy) was administered. Post-NCRT, patients were assessed for non-CCR and stratified into two groups: the SCI group received two additional cycles of chemotherapy and tislelizumab (200 mg intravenously every 3 weeks) before surgery, while the DS group proceeded to surgery. The primary endpoint was pCR rate, secondary endpoints included major pathological response (MPR) rates and safety. **Results:** Eighty-seven non-CCR pts were included (SCI: n = 54; DS: n = 33). The median age was 63 years, with 78.0% male patients. Most patients were stage IIIB(83.9%). Surgery rates were 85.2% in the SCI group (46/54) and 81.8% in the DS group (27/33). In the ITT population, SCI significantly improved pCR rates (40.7% [22/54] vs. 18.1% [6/33]; OR: 3.06, p = 0.024, , one-sided Fisher's Exact Test) and showed a trend toward higher MPR rates (51.8% [28/54] vs. 33.3% [11/33]; OR: 2.14, p = 0.071). In the PP population, pCR rates remained higher in SCI (47.8% [22/46] vs. 22.2% [6/27]; OR: 3.16, p = 0.026) and showed higher MPR rates (60.9% [28/46] vs. 40.7% [11/27]; OR: 2.02, p = 0.078) . At 12 months, PFS rates were 95.6% in the SCI group versus 77.3% in the DS group (p = 0.094) in the ITT population, and 97.4% versus 77.8% (p = 0.064) in the PP population. SCI-related adverse events included lymphopenia (97.7%), leukopenia (84.6%), and fatigue (50.0%). In the no-surgical pts in SCI group, three cases experienced immune pneumonitis and thyroid dysfunction, respectively. Treatment-related adverse events in the SCI group included lymphopenia (97.7%), leukopenia (84.6%), and fatigue (50.0%).The main postoperative complications in the SCI group and DS group were anastomotic leakage and recurrent laryngeal nerve injury (3/46 vs. 2/27, P = 0.629). No significant treatment-related adverse events occurred in the SCI group. **Conclusions:** This pioneering study demonstrates that SCI as a bridging strategy significantly improves pCR rates by >2-fold (OR>3) and shows promising PFS trends with manageable toxicity in non-CCR LA-ESCC, challenging the immediate surgery paradigm. These results warrant validation in randomized phase 3 trials to redefine standard-of-care. Clinical trial information: NCT05189730. Research Sponsor: None.

Tumor-informed liquid biopsy in predicting recurrence in patients with operable gastroesophageal adenocarcinoma: The LIQUID study.

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Background: Gastroesophageal cancers (GEC) shows high recurrence rates after curative surgery with or without perioperative/adjuvant chemotherapy. Pathological stage is currently the only prognostic tool, but its accuracy should be improved. Liquid biopsy, analyzing circulating tumor DNA (ctDNA), offers a non-invasive method to detect molecular residual disease (MRD) and monitor disease status. The LIQUID study aimed to evaluate the prognostic utility of liquid biopsy in GC patients, for whom observational studies are still scarce. **Methods:** This single-institutional study enrolled patients with resectable GC treated or not with perioperative/adjuvant chemotherapy. Liquid biopsies were collected before neoadjuvant chemotherapy (optional), pre- and post-surgery (minimum 2 weeks interval) and every six months during follow-up, until disease progression or the last follow-up for alive and progression-free patients. MRD analysis was performed using a clinical trial assay based on the tumor-informed ctDNA assay FoundationOne®Tracker, which identified somatic mutations by tissue comprehensive genomic profiling and tracked them in patients' plasma samples. **Results:** Between December 2019 and February 2024, 119 patients were enrolled. Of these, 40 were excluded due to screen failure (mostly peritoneal disease at surgery), and 27 due to technical failure (n = 18) or loss to follow-up (n = 9), leaving 52 patients (median 4 timepoints per patient) for analysis. Median age was 70 years (range: 23–86), with 55.8% male, and 86.5% of tumors located in the stomach. Pathological staging revealed pT0 (3.8%), pT1 (21.2%), pT2 (21.2%), pT3 (34.6%), and pT4 (19.2%) tumors, with nodal involvement in 69.6%. Additionally, 51.9% and 46.2% of patients received neoadjuvant or adjuvant treatment respectively, and 32.7% experienced peritoneal relapse. ctDNA presence was not significantly associated with known clinico-pathological baseline risk factors, except for postoperative N-stage ($p = 0.04$). With a median follow-up of 49.0 months (IQR 30.6 -54.0), post-surgery MRD+ patients had a significantly worse relapse-free survival (RFS) than those with ctDNA- (13.2 months vs not reached; HR 2.81 95% CI 1.23-6.45; $p = 0.011$). Similar results were observed in longitudinal ctDNA monitoring, (RFS 16.3 months for ctDNA+ vs not reached for ctDNA-; HR 2.70, 95% CI 1.22–5.97, $p = 0.011$). Notably, absence of ctDNA after completing the treatment plan (post-surgery or adjuvant therapy) or clearance/seroreversion after treatment were associated with significantly longer RFS ($p = 0.001$ and $p = 0.036$, respectively). **Conclusions:** Post-surgical landmark and longitudinal ctDNA detection demonstrates robust evidence of MRD and identifies GC patients at high risk of relapse. These findings support ctDNA as a valuable tool for postoperative surveillance and early intervention strategies in GEC. Research Sponsor: None.

Recurrence-free survival as a surrogate endpoint for overall survival in resectable esophageal cancer: An individual patient data analysis of phase III RCTs.

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Background: Overall survival (OS) is regarded as the gold standard efficacy endpoint but requires long follow-up. This study aimed to determine the validity of recurrence-free survival (RFS) as a surrogate endpoint for OS in resectable esophageal cancer. **Methods:** A systematic review of phase III randomized controlled trials (RCTs) comparing perioperative treatments for resectable advanced esophageal and gastroesophageal junction cancer was conducted. Individual patient data (IPD) were requested from all included trials. Surrogacy between RFS and OS was assessed at the individual level using the Kendall rank correlation coefficient (τ) and at the trial level using the coefficient of determination (R^2) from a meta-regression model. A τ of 0.8 and an R^2 of 0.65 were considered thresholds indicative of a good surrogate endpoint. **Results:** Twenty-two eligible trials were identified by the systematic review, and IPD were available from 10 RCTs (JCOG1109, JCOG9907, JCOG9204, FFCD9901, FFCD9102, SAKK75/08, CROSS, KOK, NeoRes2 and CMISG1701), including 2,145 patients who underwent R0 resection (cStage IV, cT1N0 and cT4b excluded). Of these, 1563 patients had squamous cell carcinoma, and 575 patients had adenocarcinoma. The 5-year OS and RFS rates were 53.2% and 46.2%, respectively, with a median OS of 6.2 years and a median RFS of 3.6 years. For individual-level surrogacy, Kendall's τ was 0.823 (95% CI: 0.807–0.839). Subgroup analysis based on treatment modality revealed τ values of 0.830 (95% CI: 0.800–0.861) for patients receiving neoadjuvant chemotherapy (NAC; n = 586), 0.827 (95% CI: 0.803–0.850) for those receiving neoadjuvant chemoradiotherapy (NACRT; n = 982), 0.770 (95% CI: 0.713–0.828) for the surgery-alone group (n = 320), and 0.861 (95% CI: 0.824–0.898) for the adjuvant chemotherapy group (n = 257). Trial-level surrogacy analysis across all 22 trials demonstrated an R^2 of 0.735 (95% CI: 0.512–0.939). The surrogate threshold effect was 0.929, indicating the minimum RFS treatment effect required to predict a nonzero effect on OS. **Conclusions:** This study demonstrated strong individual-level and trial-level surrogacy between RFS and OS in surgically resectable esophageal cancer across all perioperative treatment modalities. These findings hold promise for expediting the development of novel perioperative treatment by shortening the follow-up of clinical trials on esophageal cancer. Research Sponsor: None.

4069 Poster Session

Neoadjuvant toripalimab plus CapeOX in patients with locally advanced EBV-positive gastric or esophagogastric junction adenocarcinoma (GC/EGJC): Results from the phase II NICE trial.

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Background: Surgery remains the cornerstone of curative therapy for locally advanced GC/EGJC. EBV-positive tumor is a distinct molecular subtype that would be potentially sensitive to immunotherapy, but no consistent reports. Given that chemotherapy may enhance antitumor immunity, perioperative immunochemotherapy may be a promising modality for EBV-positive patients. **Methods:** The NICE trial is a multicenter, multi-cohort phase II study (NCT04744649) evaluating the safety and efficacy of toripalimab plus CapeOX as perioperative treatment in patients with locally advanced GC/EGJC. The Cohort B was first of its kind to assess the efficacy of the immunochemotherapy on the EBV-positive GC/EGJC , in which patients received toripalimab (240 mg) combined with standard-dose CapeOX every 3 weeks for 4 cycles preoperatively and 4 cycles postoperatively. Eligibility criteria included clinical tumor stages of cT3-4aNxM0 or cT2N+M0 disease as determined by both imaging scan and staging laparoscopy with negative peritoneal cytology. The primary endpoint was major pathologic response (MPR, defined as $<$ 10% viable tumor cells). The tumor immune microenvironment (TIME) of tissue samples obtained before and after treatment was analyzed using multiple immunofluorescence assays to assess changes in immune cell infiltration and other biomarkers related to treatment response. **Results:** From May 2021 to September 2023, 17 patients with EBV-positive GC/EGJC (GC, n = 15; EGJC, n = 2) were enrolled, with cT2N0 (n = 1), cT3N1-3 (n = 5), and cT4aN1-3 (n = 11). All patients completed 4 preoperative cycles of treatment, and none experienced progression before surgery. Only one patient withdrew the inform content after preoperative therapy, the 16 patients underwent radical resection, achieving a 100% R0 resection rate (16/16). The MPR rate was 37.5% (6/16), and pathological complete response rate (pCR) was 25.0% (4/16). Of the 16 participants, 15 received postoperative adjuvant therapy, while 1 declined further treatment. The TIME analysis results showed that tumor-infiltrating CD8+ T cells in post-treatment tumor tissues significantly clonally expanded compared with pre-treatment paired tissues. Treatment-related grade 3/4 adverse events were observed in 6 patients (35.3%, 6/17). Until Dec 31 2024, none of the patients experienced disease recurrence. **Conclusions:** Neoadjuvant toripalimab combined with CapeOX is a safe and effective treatment option for patients with EBV-positive, locally advanced GC/EGJC, with moderate MPR and pCR, indicating further investigating for this distinct type of cancer. Clinical trial information: NCT04744649. Research Sponsor: None.

Early detection and neoadjuvant efficacy prediction for esophageal cancer using cfDNA methylation-based liquid-biopsy assay.

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Background: Esophageal cancer (EC) is a major malignancy of the upper gastrointestinal tract globally. Early detection and timely therapeutic intervention are pivotal in improving patient outcomes. However, current diagnostic methods often fail to detect EC at an early stage and lack the ability to predict treatment response. There is an urgent need for non-invasive, sensitive, and specific biomarkers to enhance early detection and guide personalized treatment strategies. This study aims to develop a tool to detect EC and predict the neoadjuvant efficacy. **Methods:** This is a prospective multicenter diagnostic study. From July 2023 to October 2024, a total of 236 esophageal cancer cases (stage I: 19.9%, stage II: 24.6%, stage III: 39.4%, stage IV: 16.1%), 31 chronic esophagitis cases, and 441 healthy controls were enrolled from multiple centers. Methylation features and fragmentomic characteristics derived from methylation sequencing data were integrated to develop a gradient-boosted tree model. A nested cross-validation framework was employed to ensure robustness and reliability. Additionally, predictive models for therapeutic responses to neoadjuvant treatment were constructed. **Results:** The detection model achieved an area under the curve (AUC) of 0.954 (95% CI: 0.936-0.971. At a specificity of 97.9% (95% CI: 96.1%-99.0%), the overall sensitivity reached 84.7% (95% CI: 79.5%-89.1%) , with stage-specific sensitivities of 69.5% for early-stage (I/II) and 97% for advanced-stage (III/IV) disease. The detection model maintained robust performance across various clinicopathological parameters, including differentiation grade, neural invasion, vascular invasion, tumor count, and tumor location, with no significant differences in subgroup performance. Among the cohort, 44 patients underwent neoadjuvant therapy, with 90.9% (40/44) receiving immunochemotherapy. The major pathological response (MPR) rate was 52.3% (23/44) and the pathological complete response (pCR) rate was 15.9% (7/44). No clinical features were found to correlate with MPR or pCR rates. Differential methylation profiles between MPR/pCR and non-MPR/pCR patients were analyzed to construct predictive models for neoadjuvant therapy outcomes. Using logistic regression and leave-one-out cross-validation, the MPR prediction model achieved an accuracy of 86.3%, while the pCR prediction model demonstrated an accuracy of 90.9%. **Conclusions:** Our cfDNA-methylation based assay demonstrated high performance in early EC detection and promising value in predicting neoadjuvant therapy responses. This non-invasive approach has the potential to revolutionize EC management by enabling earlier diagnosis and personalized treatment strategies. Research Sponsor: None.

Effectiveness of a multidomain mHealth-based intervention in enhancing recovery and quality of life for esophageal cancer patients undergoing esophagectomy.

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Background: Esophagectomy, a primary treatment for esophageal cancer (EC), often compromises patients' quality of life (QOL), leading to malnutrition, reduced physical function, and psychological distress. Multidomain mHealth-based interventions, which leverage technology to deliver comprehensive nutritional, physical, and psychological support, offer a promising approach to address these challenges during prehabilitation and Enhanced Recovery After Surgery (ERAS) phases. Despite their potential, high-quality evidence demonstrating their effectiveness remains limited. This study evaluates the effectiveness of a multidomain mHealth intervention on QOL and recovery outcomes in EC patients undergoing esophagectomy. **Methods:** Between April 27, 2021 and June 30, 2023, this single-center, randomized controlled trial was conducted, enrolling 76 patients with pathologically confirmed EC scheduled for esophagectomy. Participants were randomized to either a multidomain mHealth-based intervention group (n = 38) or a usual care group (n = 38). The intervention delivered tailored nutritional, physical, and psychological support via a self-developed WeChat-based management platform, spanning from 2 weeks pre-admission to 11 weeks post-discharge. The primary outcome was the change in QOL, assessed using the EORTC QLQ-C30 and QLQ-OES-18. Secondary outcomes included changes in nutritional status (e.g., weight), physical fitness (e.g., 6-minute walk distance), and psychological health (e.g., PHQ-9, GAD-7, SCSQ-20). Outcomes were assessed at baseline, hospital admission, and 3 and 11 weeks post-discharge. **Results:** At 11 weeks post-discharge, the intervention group showed a significant improvement in QOL, with a 15.56-point increase in Global Health Status (EORTC QLQ-C30) compared to a 5.91-point decline in the usual care group (difference: 21.47 points; 95% CI: 9.86–33.08; $p < 0.001$). Functional and symptom scores, including social functioning, appetite, and eating, improved markedly in the intervention group. The intervention group also demonstrated superior outcomes in weight change (+2.19 kg; 95% CI: 0.09–4.30; $p = 0.041$) and 6-minute walk distance (+80.65 meters; 95% CI: 41.64–119.66; $p < 0.001$). Psychological well-being improved significantly, with reductions in PHQ-9 (-4.70; 95% CI: -6.59 to -2.80; $p < 0.001$) and GAD-7 (-4.63; 95% CI: -6.52 to -2.74; $p < 0.001$), and an increase in positive coping scores (+11.83; 95% CI: 7.20–16.45; $p < 0.001$). **Conclusions:** This multidomain mHealth intervention significantly enhanced QOL, nutritional and physical outcomes, and psychological health in EC patients undergoing esophagectomy. These findings underscore the potential of mHealth platforms to optimize prehabilitation and recovery, offering a scalable and impactful approach to improving outcomes in oncology care. Clinical trial information: ChiCTR2100045650. Research Sponsor: None.

Exome analysis of over 5000 esophagogastric cancers.

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Background: Esophagogastric cancers (EGCs) encompass a heterogenous group of cancers. The genomic drivers that overlap or differentiate among each cancer type are not well studied, despite the availability of therapies that target specific genetic alterations in driver genes. **Methods:** Genomic data from Natera's Real-World Database (N = 5,872) was analyzed to investigate genomic patterns in EGC patients (09/2019-11/2024) receiving standard-of-care treatment. This exploratory analysis was conducted on tumor tissue data available from whole-exome sequencing, generated as part of SignateraTM testing.Microsatellite instability (MSI) status was determined using the MSIsensor and 96-trinucleotide contexts and was correlated with COSMIC SBS signatures (v3.3). Prevalence analysis included only non-synonymous mutations, with ranking adjusted for gene length. **Results:** Patients included 4050 men and 1822 women, with median age 65.3 years, and stage distribution as follows: I: 7.9%, II:14.7%, III: 32.9%, IV: 32.2%, and 12.3% unknown. Gastric cancer (GC) was most common (48.1%), followed by esophageal (EC, 45.9%) and gastroesophageal junction (GEJ, 7.2%). MSI-high cases (7.7% prevalence overall, 2.2% in squamous EC, 5.2% in EC adenocarcinoma, 6.1% in GEJ, 10.9% in GC) had a distinct mutational landscape with frequent missense deletions. The most common signatures were clock-like (SBS1, SBS5), MMR-deficiency-related (SBS6, SBS15), and Thiopurine-chemotherapy-related (SBS87). *PIK3CA* mutations were found in 7.9% of cases, with the most common being E545 (2.6%), H1047 (1.1%), and E542 (1.0%). Notably, *PIK3CA* exon 9/20 mutations displayed a trend of higher prevalence in ctDNA-positive cases. **Conclusions:** These data provide insights into the mutational landscape of EGC and enhance our understanding of differences between histological subtypes. Future studies will continue to explore the associations between genomic subtypes, treatment patterns, and clinical outcomes.
Research Sponsor: None.

Top mutated genes and variants in esophagogastric cancers.

Group	N	Genes	Variants
EGC, all	5872	*TP53* (49.8%) *ARID1A*(16.1%)	*ACVR2A* K437X (5.5%) *RPL22*K15X (5.3%) *RNF43*G659X (4.0%)
EGC, MSS	5411	*TP53* (47.9%) *ARID1A*(11.9%)	*G2E3* T361fs (3.1%) *TP53*R175H (2.7%) *LRRIQ3*Q245fs (2.3%)
EGC, MSI-high	422	*ARID1A* (71.7%) *KMT2D*(68.7%) *RPL22*(60.3%)	*ACVR2A* K437X (58.6%) *RPL22*K15X (56.6%) *RNF43*G659X (44.1%)
GEJ, MSS	448	*TP53* (50.5%) *CSMD1*(13.4%) *PCLO*(12.0%)	*TMBIM4* Y174fs (3.2%) *TP53*R273C (3.2%) *TP53*R175H (3.2%)
GC, MSS	2487	*TP53* (33.5%) *CDH1*(14.4%) *ARID1A*(13.8%)	*G2E3* T361fs (3.1%) *PIK3CA*E545K (2.3%) *LRRIQ3*Q245fs (2.2%)
EC Adenocarcinoma, MSS	1599	*TP53* (33.5%) *CDKN2A*(13.5%) *ARID1A*(12.6%)	*TP53* R175H (4.0%) *TP53*R248Q (3.4%) *G2E3*T361fs (3.1%)
EC Squamous carcinoma, MSS	348	*TP53* (61.8%) *NOTCH1* (17.2%)	*PIK3CA* E545K (3.9%) *TMBIM4*Y174fs (3.4%) *TP53*Y220C (2.9%)

The lost evidence: A phase III, multicenter randomized controlled trial of neoadjuvant chemotherapy paclitaxel plus cisplatin versus surgery alone for stage IIA–IIIB esophageal squamous cell carcinoma.

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Background: The efficacy of neoadjuvant chemotherapy (NAC) vs primary surgery alone for treatment of locally advanced esophageal squamous cell carcinoma (ESCC) remain controversial between Western and Eastern countries. The daily NAC practice in China was without the high level evidence. The Esophageal Cancer Committee of the China Anti-Cancer Association tried to connect the the lost chain of evidence. To compare safety and long-term survival of NAC followed by surgery with that of surgery alone. **Methods:** A prospective, multicenter, open-label, randomized phase III clinical trial that compared safety and efficacy of NAC vs primary surgery for ESCC. From July 18, 2015, to March 29, 2018, we enrolled 605 clinical stage IB-III thoracic ESCC (excluding stage T4b, N3, 7th UICC-TNM staging, 2009). They were randomized to NAC plus surgery (group NAC; n=304) or primary surgery alone (group S; n=301). In group NAC, paclitaxel 175 mg/m2 intravenously (IV) and cisplatin 75 mg/m2 every 3 weeks for two cycles. All patients underwent McKeown, Ivor Lewis or minimally invasive esophagectomy and extended 2-field lymph node dissection. The primary outcome was 5-year overall survival (OS). Secondary outcomes included disease free survival (DFS), R0 resection rate, pathologic complete response rate and toxicities. The intention-to-treat principle was followed for analysis. The SPSS, version 23.0 (IBM Corp). The statistically significant was assumed as a 2-sided $P<0.05$. The Kaplan-Meier method was used to calculate OS and DFS with the log-rank test. The last follow-up data was April 12, 2024. The 5-year OS of primary surgery was 30%. A 5-year survival with a 12% increase for the NAC group was assumed. The sample size was calculated with a two-sided alpha level of 5%, a power of 80%, an expectation of 2 years accruement and a 5-year followup period. The total sample size was set at 528 patients with 10% of patients lost to follow-up. **Results:** Among 605 patients (432 men [71.4%]; mean [SD] age, 61.7 [7.9] years; most frequent clinical stages IIIA 170 [30.2%]), Leukopenia (28%) and neutropenia (49.8%) were the most common grade 3 or 4 adverse events during NAC. Complications was similar between the 2 groups based on Clavien-Dindo classification. The 90-day perioperative mortality rate was 1.6% for the NAC group (4 of 244) and 2.2% for the Surgery alone group (6 of 268) (P = 0.754). The pathologic complete response rate was 6.58% (20 of 304) in NAC group. NAC group had a higher R0 resection rate (98.8% v 98.5%; P > 0.999), a better 5 years OS rate (61.1% vs 51.6%; hazard ratio, 0.79; 95% CI, 0.63 to 1.0; P = 0.0469), and a prolonged DFS (58.5% vs 46.2% months; hazard ratio, 0.71; 95% CI, 0.56 to 0.91; P=0.0067). 0.71 (0.56,0.91). The max follow up period of NAC group was 110 months, S group 105 months. The median follow up period of NAC group was 79.4, whereas 55.2 in surgery group. **Conclusions:** This trial showed that NAC plus surgery improves survival over surgery alone among patients with locally advanced ESCC, with acceptable and manageable adverse events. Clinical trial information: NCT02395705. Research Sponsor: None.

An interim analysis of phase III study on neoadjuvant chemotherapy versus perioperative toripalimab plus neoadjuvant chemotherapy for locally advanced esophageal squamous cell carcinoma: Henan Cancer Hospital Thoracic Oncology Group 1909 (HCHTOG1909).

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Background: In the era of immunotherapy, whether neoadjuvant immunochemotherapy (NAIC) would be standard treatment of locally advanced esophageal squamous cell carcinoma (ESCC) is without conclusion. The HCHTOG1909 was aimed to compare the safety and long-term efficacy of NAIC followed by minimally invasive esophagectomy (MIE) with those of neoadjuvant chemotherapy followed by MIE. This second interim analysis was aim to compare the short term results of two groups. **Methods:** A prospective, single-center, open-label, randomized phase III clinical trial. Between May 15, 2020 and April 23, 2024, 401 resectable ESCC with clinical stage T1N1-3M0 to T2-3N0-3M0 were enrolled(8th UICC-TNM), 196 in the toripalimab group and 205 in the chemotherapy group. The patients receive either neoadjuvant paclitaxel (175 mg/m2) and cisplatin (75 mg/m2) plus toripalimab (240mg) (toripalimab group) or paclitaxel and cisplatin alone (chemotherapy group) every 3 weeks for 2 cycles. After MIE, the toripalimab group received toripalimab (240 mg every 3 weeks for up to 6 months). The event-free survival (EFS) was the primary endpoint. The pathological complete response (pCR) was the key secondary endpoints. Other endpoints included postoperative complications, mortality, adverse events, overall survival and disease free survival. We planned 3 interim analyses. This was a planned second interim analysis. The sample size was calculated based on the primary endpoint EFS. The hazard ratio assumed to be 0.68 between two groups. A type I error allocated (two-sided) 0.05, 90% power and drop-out rate of 10% in 5 years. The χ^2 test and the Fisher exact test was employed for categorical parameters, the t test or analysis of variance was adopted for continuous variables. **Results:** Among 401 patients (305 men [76.1%]; mean [SD] age, 70.7 [3.5] years; most frequent clinical stages III 213 [53.1%]). The toripalimab group had a higher pCR rate (26.1% vs. 6.2%; $P < 0.001$). The 90-day perioperative mortality rate was 2.42%(4) for the toripalimab group and 2.5%(4) for the chemotherapy alone group ($P = 0.9790$). The most frequent irAE was hypothyroidism. There was no significant difference observed for postoperative complication rate ($P = 0.453$). The grade 3 or 4 treatment-related adverse events did not differ between the two groups (13.8% versus 10.8%). **Conclusions:** The interim results of HCHTOG1909 showed the addition of perioperative toripalimab to NAC is safe in resectable ESCC, and the pCR rate is significantly improved. Clinical trial information: NCT04280822. Research Sponsor: None.

Circulating tumor DNA (ctDNA) analysis for improved treatment response assessment and prediction of clinical outcomes in patients with esophageal cancer.

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Background: Despite curative-intent treatment, patients with esophageal cancer experience a high risk of recurrence, and optimal patient management is limited by poor risk stratification and treatment response assessment strategies. ctDNA has demonstrated value as a prognostic biomarker in esophageal cancer; however, improved analytical and clinical performance of ctDNA analysis is necessary to reliably support patient management decisions in clinical practice. **Methods:** Between September 2017 and June 2023, plasma samples were collected from patients with esophageal cancer before, during, and after standard of care treatment in the routine care setting. In this retrospective analysis, ctDNA testing was performed on a subset of patients using a next-generation tumor-informed assay interrogating up to 50 personalized variants (Haystack MRD, Quest Diagnostics). **Results:** ctDNA was assessed in 149 samples from 51 patients with stage I-III esophageal adenocarcinoma (n= 40) or squamous cell carcinoma (n= 11). Fifteen patients with clinical follow-up (FU) available at the time of analysis had at least one sample collected after curative-intent treatment [neoadjuvant chemoradiotherapy (nCRT) and surgery (n=10) or definitive CRT (n=5)]. ctDNA was detected (ctDNA+) following curative-intent treatment in 5/15 (33%) patients, all 5 (100%) of whom experienced disease recurrence or were deceased at FU (median time from ctDNA+ result to FU: 14.4 months, range: 0.1-24.5). Of the 10 (67%) patients with no ctDNA detected (ctDNA-) following curative-intent treatment, 7 (70%) were disease-free at FU (median time from ctDNA- result to FU: 46.7 months, range: 6.3-65.5). In the neoadjuvant setting, paired pre- and post-nCRT samples were evaluated in 18 patients, demonstrating ctDNA detection in 18/18 (100%) patients prior to nCRT versus 8/18 (44%) following nCRT. ctDNA positivity following nCRT was strongly associated with poor pathological response (p=0.0026), and ctDNA dynamics observed longitudinally during nCRT served as a robust indicator of response. Of note, one patient experienced metastatic progression during nCRT, discovered at surgery, and ctDNA levels in this patient increased 550-fold while on nCRT. **Conclusions:** Evaluation of ctDNA using a next-generation tumor-informed platform supports improved response assessment to nCRT as well as accurate risk stratification following curative-intent treatment in patients with esophageal cancer. ctDNA positivity following curative-intent treatment predicted disease recurrence with a lead time of up to 22 months. Additional analyses are ongoing to further validate these findings. Research Sponsor: None.

Clinical implication of MDM2 amplification in advanced biliary tract cancer (BTC): A propensity score-matched, retrospective cohort study of 813 patients.

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Background: Restoring p53 tumor suppressor activity by blocking the interaction between p53 and MDM2, its endogenous negative regulator, has emerged as a potential therapeutic target for several tumors including BTC. However, the frequence and clinical implication of MDM2 amplification (amp) has not been investigated for BTC. **Methods:** Patients with unresectable or metastatic BTC who had available tissue-based targeted next generation sequencing (NGS) data and were treated with first-line gemcitabine plus cisplatin (GemCis)-containing chemotherapy at Asan Medical Center, Seoul, Korea between January 1, 2016, and December 31, 2023, were included. MDM2-amp was defined 5 or greater copies per tumor cell. Baseline characteristics and clinical outcomes to GemCis-containing therapy were compared according to the presence of MDM2-amp/TP53 wild-type (WT). Propensity score matching (PSM) with a 1:4 ratio was performed to balance the baseline characteristics between the patients with and without MDM2-amp/TP53-WT. **Results:** Among 813 patients, 41 (5.0%) had MDM2-amp/TP53-WT and there was no significant association with primary tumor sites: 4.7% in intrahepatic cholangiocarcinoma, 3.7% in extrahepatic cholangiocarcinoma, and 8.0% in gallbladder cancer (p=0.111). Patients with MDM2-amp/TP53-WT significantly had less frequent viral hepatitis B infection (2.4% vs. 18.4%, p=0.009) and lung metastasis (2.4% vs. 13.2%, p=0.043); otherwise, no significant association with baseline characteristics was noted. After PSM (40 for MDM2-amp/TP53-WT vs. 155 for non-MDM2-amp/TP53-WT), patients with MDM2-amp/TP53-WT showed significantly longer progression-free survival compared to those in the matched group (median, 9.6 vs. 6.9 months; p=0.034) and non-significant tendency toward longer overall survival (median, 20.3 vs. 16.4 months; p=0.103). **Conclusions:** In patients with unresectable or metastatic BTC, MDM2-amp/TP53-WT occurred in 5% and it was associated with better survival outcomes of first-line GemCis-containing chemotherapy. Our findings suggest that MDM2-amp/TP53-WT serves as a biomarker for a distinct subgroup of BTC, warranting active investigation into MDM2 inhibitors. Research Sponsor: Boehringer Ingelheim.

Real-world outcomes of first-line therapies for unresectable hepatocellular carcinoma in the United States.

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Background: Unresectable hepatocellular carcinoma (uHCC) remains a significant clinical challenge despite advances in systemic therapies. Real-world evidence complements clinical trials by evaluating treatment effectiveness in diverse patient populations. This study assessed real-world progression-free survival (rwPFS) and overall survival (rwOS) for current standard-of-care first-line (1L) systemic therapies for uHCC. **Methods:** This retrospective study used the Flatiron Health database and included untreated uHCC patients diagnosed on or after January 1, 2018, who initiated 1L systemic therapies (atezolizumab + bevacizumab [atezo + bev], lenvatinib, sorafenib, or durvalumab + tremelimumab [durva + treme]) on or after May 29, 2020. Baseline characteristics, including ECOG status, ALBI grade, and demographic factors, were reported across cohorts. Kaplan-Meier method was used to estimate rwPFS and rwOS for each cohort. **Results:** A total of 1,539 patients were included: atezo + bev (n = 1,070), durva + treme (n = 238), lenvatinib (n = 139), and sorafenib (n = 92). Baseline characteristics were similar across cohorts. Most patients had ECOG (Eastern Cooperative Oncology Group) status 0–1 (57%–70%), with 15%–21% having ECOG 2+. ALBI (Albumin-Bilirubin) grade 2 was observed in 41%–60% of patients, while ALBI grade 3+ was present in 8.1%–17%. The median rwPFS for atezo + bev, lenvatinib, and durva + treme were similar at 4.7 months (95% CI: 4.1–5.4), 4.6 months (95% CI: 3.8–5.5), and 4.2 months (95% CI: 3.2–5.7), respectively. Sorafenib had a significantly shorter rwPFS at 3.0 months (95% CI: 2.5–4.4). The median rwOS for atezo + bev, lenvatinib, and sorafenib were similar at 10.7 months (95% CI: 9.5–11.8), 10.4 months (95% CI: 7.8–13.4), and 10.5 months (95% CI: 5.6–14.9). Durva + treme had a significantly shorter rwOS at 7.6 months (95% CI: 5.7–18.6). At 12 months, the survival probabilities for rwOS were 45% (95% CI: 42%, 48%) for Atezo + Bev, 41% (95% CI: 33%, 50%) for Durva+Treme, 45% (95% CI: 36%, 55%) for lenvatinib, and 43% (95% CI: 33%, 56%) for sorafenib. At 24 months, survival probabilities for rwOS were 27% (95% CI: 24%, 31%) for Atezo + Bev, 26% (95% CI: 19%, 36%) for lenvatinib, 21% (95% CI: 12%, 35%) for sorafenib, and data were undetermined for Durva + Treme. **Conclusions:** Findings from this real-world analysis show that atezo + bev demonstrated comparable outcomes versus lenvatinib, and potential benefits in rwPFS versus sorafenib and rwOS versus durva + treme. The median rwOS was approximately 10 months across treatments and highlights the need for novel therapies to improve long-term survival in uHCC. These results underscore the importance of evaluating treatment effectiveness in real-world populations, which may differ from clinical trial cohorts. Further analyses are warranted to explore these findings and optimize treatment strategies for uHCC. Research Sponsor: Bristol Myers Squibb.

First-line rilvegostomig (rilve) plus chemotherapy (CTx) in advanced biliary tract cancer (BTC): Primary analysis of GEMINI-Hepatobiliary substudy 2 Cohort A.

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Background: Immune checkpoint inhibitors plus CTx have improved outcomes in first-line advanced BTC (median progression-free survival [PFS] 6.5–7.2 months), but survival remains limited. Rilve, an anti-PD-1/TIGIT bispecific antibody, may provide benefit by targeting two immune checkpoints. GEMINI-Hepatobiliary (NCT05775159) is a phase 2 study evaluating rilve or volrustomig alone or in combination regimens in patients (pts) with advanced hepatocellular carcinoma (substudy 1) or BTC (substudy 2). We report data from Cohort A (rilve plus CTx) in substudy 2. **Methods:** Pts aged ≥18 years with previously untreated unresectable/metastatic BTC and an ECOG performance status 0–1 received rilve every 3 weeks (Q3W) for up to 2 years plus gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2 on days 1 and 8 Q3W for up to 8 cycles. Coprimary endpoints were investigator-assessed 6-month PFS per RECIST v1.1 and safety and tolerability; secondary endpoints included median PFS, objective response rate (ORR), duration of response (DoR; all investigator-assessed per RECIST v1.1), and pharmacokinetics (PK). Tumoral PD-L1 expression, peripheral PD-1 and TIGIT receptor occupancy (RO), and T cell profiles were also evaluated. **Results:** Thirty pts were treated; median age was 60 years, 70.0% were Asian, and 83.3% had metastatic disease. As of Nov 4 2024, the median follow-up in all pts was 6.9 months (interquartile range 5.6–9.5) and rilve treatment was ongoing in 36.7% of pts. Efficacy and safety data are shown in the Table. The 6-month PFS rate was 73.0%; median PFS was 8.3 months. Median PFS was numerically longer in pts with PD-L1 tumor area positivity ≥1% (9.4 months, n = 18) vs the overall study population. The safety profile was manageable and consistent with prior studies. Rilve exposure was consistent with historical monotherapy data, indicating an absence of PK drug interactions and cross-indication differences. Rilve achieved ≥90% PD-1 and TIGIT RO on peripheral T cells and induced peripheral T cell proliferation. **Conclusions:** Rilve plus CTx demonstrated promising efficacy with a manageable safety profile and sustained target engagement. Longer follow-up for data maturity is warranted. Phase 3 studies with rilve in BTC (ARTEMIDE-Biliary 01; DESTINY-BTC01) are ongoing. Clinical trial information: NCT05775159. Research Sponsor: AstraZeneca.

	N=30*
PFS	
Events in all dosed pts, n (%)	19 (63.3)
6-month rate, % (95% CI)	73.0 (53.2–85.5)
Median, months (95% CI)	8.3 (6.7–9.6)
ORR, % (95% CI)	31.0 (15.3–50.8)
Best overall response, n (%)	
Partial response	9 (31.0)
Stable disease	18 (62.1)
Progressive disease	2 (6.9)
Median DoR, months (95% CI)	6.9 (2.8–not calculated)
Any / rilve-related AEs, n (%)	30 (100) / 21 (70.0)
Grade ≥3	26 (86.7) / 4 (13.3)
Serious AEs	12 (40.0) / 2 (6.7)
Leading to rilve discontinuation	1 (3.3) / 0
Leading to death	2 (6.7) / 0

*N=29 for response outcomes.
AE, adverse event; CI, confidence interval.

Combined treatment of durvalumab, bevacizumab and tremelimumab in subjects with hepatocellular carcinoma (HCC) or biliary tract carcinoma (BTC).

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Background: Anti-VEGF in combination with anti-PD1/PD-L1 represents a synergistic therapeutic strategy that has demonstrated efficacy, prolonging survival in cancers like HCC, RCC, and NSCLC. This combination induces modifications in the tumor microenvironment, leading to a reduction in immunosuppressive cells, improved dendritic cell maturation, antigen presentation, downregulation of immune checkpoint molecules, and enhanced T-cell activity. Combining CTLA-4 inhibitors with anti PD-1/PD-L1 enhances T-cell mediated anti-tumor responses by leveraging distinct yet complementary mechanisms. Targeting VEGF, PD-L1, and CTLA-4 pathways simultaneously in HCC and BTC provides a novel approach that hasn't been tested in clinical trials. Our group previously reported *in vivo* activity in murine BTC models and preliminary clinical results supporting this triplet combination in BTC. The aim of this study is to determine if VEGF inhibition with anti-CTLA-4 and anti-PD-LI therapy augments antitumor immunity and clinical responses in HCC and BTC patients. **Methods:** This was a Phase II trial conducted to evaluate efficacy of durvalumab, bevacizumab and tremelimumab in advanced HCC BCLC stage C or BTC. Participants received bevacizumab at 7.5mg/kg and durvalumab 1150mg every 3 weeks by IV infusion on Day 1 of Cycle 1 (durvalumab) and Day 1 of Cycle 2 (bevacizumab). Tremelimumab at a dose of 300mg was administered by IV infusion only once on Day 1 of Cycle 1. The combination of durvalumab and bevacizumab continued in 3-week cycles until disease progression or unacceptable toxicity. Primary endpoint was 6-month progression-free survival (PFS) and secondary endpoints were safety, overall survival (OS) and best overall response (BOR). Correlative studies assessing immune response were performed. **Results:** Between March 2021 and August 2024, 27 patients were enrolled (HCC: 6pts, BTC: 21pts). The median age was 66y (39-80) and 62% were male. 37% of the patients enrolled received prior ICI. As of November 4th, 2024, with a median follow-up of 8mos, mPFS was 3.5mos and mOS 9.5mos in all 27 efficacy-evaluable pts. The estimated 6 months PFS rate was 37%. The BOR was partial response in 4 pts (18%) followed by stable disease in 9pts (40%). The most common grade 3-4 TRAEs were lymphopenia (6pts, 22%), anemia (9pts, 33%), diarrhea/colitis (7pts, 25.9%), elevated lipase (4pts, 14.8%). Treatment discontinuation related to AEs occurred in 7pts (26%). One treatment-related death occurred secondary to an upper gastrointestinal bleed. **Conclusions:** The combination of durvalumab, bevacizumab and tremelimumab did not meet its primary endpoint but demonstrated a clinically meaningful overall survival benefit. No new safety signals were seen. Clinical trial information: NCT03937830.
Research Sponsor: None.

Outcomes by baseline tumor burden using the 6-and-12 score in EMERALD-1: A phase 3 study of durvalumab (D) ± bevacizumab (B) with transarterial chemoembolization (TACE) in embolization-eligible unresectable hepatocellular carcinoma (uHCC).

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Background: In EMERALD-1 (NCT03778957), D + B + TACE significantly improved progression-free survival (PFS) vs TACE in participants (pts) with embolization-eligible uHCC. Tumor burden is a prognostic factor in HCC. Prior analyses showed improvements in PFS with D + B + TACE vs TACE in pts who met or exceeded the up-to-7 criterion (a measure based on tumor number and size), and in those with max tumor diameters of < 10 cm or ≥10 cm. The 6-and-12 score measures tumor burden based on tumor number and size. We assessed outcomes in EMERALD-1 by baseline tumor burden using the 6-and-12 score. **Methods:** Pts were randomized 1:1:1 to D + B + TACE, D + TACE, or TACE. Pts received D (1500 mg) or PBO for D (Q4W) + TACE. After completing the last TACE, pts received D (1120 mg) + B (15 mg/kg), D (1120 mg) + PBO for B, or PBOs for D and B (Q3W). In pts who received D + B + TACE and TACE, PFS, time to progression (TTP), and objective response rates (ORR), per BICR RECIST v1.1 in the intent-to-treat (ITT) population, and safety and number of TACE cycles in the safety analysis set (SAS; pts received ≥1 dose of study treatment [tx], regardless of randomization) are reported by baseline tumor burden using 6-and-12 scores: ≤6, > 6–12, or > 12. **Results:** Overall, 40.0%, 43.9%, and 16.2% of pts belonged to the ≤6, > 6–12, and > 12 groups, respectively. The number of pts who received ≥2 TACE cycles increased across the groups (≤6: 63.8%; > 6–12: 81.7%; > 12: 89.8%). PFS and TTP improved with D + B + TACE vs TACE, regardless of baseline tumor burden, with the best relative improvement in hazard ratios (HRs) in the > 12 group (Table). ORRs were higher for D + B + TACE vs TACE in all groups. Max Grade 3–4 tx-related adverse event (TRAE) frequencies were numerically higher with D + B + TACE vs TACE across tumor burden groups; differences were reduced when adjusted for exposure. No tx-related deaths occurred with D + B + TACE. **Conclusions:** PFS, TTP, and ORR benefits were seen with D + B + TACE vs TACE with manageable safety, regardless of tumor burden, further supporting a favorable risk-benefit profile with D + B + TACE in embolization-eligible uHCC. Clinical trial information: NCT03778957. Research Sponsor: AstraZeneca.

	≤6		>6–12		>12	
ITT	**D + B + TACE n=81**	**TACE n=82**	**D + B + TACE n=84**	**TACE n=95**	**D + B + TACE n=38**	**TACE n=28**
Median PFS (95% CI), months	19.4 (13.7–24.9)	11.1 (7.0–13.6)	13.9 (7.2–19.6)	9.7 (6.9–16.3)	11.1 (4.4–16.6)	4.8 (2.9–6.9)
PFS HR vs TACE (95% CI)	0.69 (0.47–1.01)		0.85 (0.59–1.22)		0.61 (0.33–1.13)	
Median TTP (95% CI), months	22.1 (15.1–30.5)	11.1 (7.0–13.9)	22.0 (13.9–27.7)	15.4 (7.2–16.7)	16.6 (6.9–25.1)	5.1 (3.0–7.1)
TTP HR vs TACE (95% CI)	0.60 (0.40–0.90)		0.66 (0.43–1.01)		0.42 (0.20–0.87)	
ORR, n (%)*	47 (58.8)	27 (33.8)	31 (36.9)	32 (33.7)	10 (26.3)	1 (3.6)
SAS	**n=71**	**n=81**	**n=61**	**n=92**	**n=22**	**n=27**
Max Grade 3–4 TRAE, n (%)	17 (23.9)	9 (11.1)	17 (27.9)	3 (3.3)	7 (31.8)	0
event rate per 100 pt-years	15.9	7.9	19.9	3.1	22.2	

*In pts with evaluable disease at baseline.

Phase I study of Ori-C101, an armored GPC3-directed CAR-T, in patients with advanced hepatocellular carcinoma (HCC).

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Background: Previously, we reported the results of Ori-C101 from investigator initiated trial in China (ChiCTR1900028121). The data demonstrated that Ori-C101 owned a favorable safety profile and promising efficacy. Among 10 $GPC3^+$ HCC patients (pts) treated with Ori-C101, 9 pts (90%) achieved disease control and 6 pts (60%) met partial response per RECIST 1.1. Two pts with PR attained progression-free survival of one and two years respectively, with an overall survival close to 3 years. These results implied that Ori-C101 potentially held significant clinical benefits. Subsequently, extensive optimizations and improvements in the manufacturing process were implemented to enhance its clinical efficacy and persistency. Hence, a multicenter registration study was launched in China (the BEACON study), and herein, we will present the preliminary results. **Methods:** This is an open-label, multi-center, dose-escalation (3+3 design) study. $GPC3^+$ advanced HCC pts who failed at least 2 lines of systemic treatments received a single hepatic arterial infusion with a total dose of 0.9 to 6×10^8 CAR-T cells. Primary endpoints are rate of dose-limiting toxicities (DLTs) and safety with the aim to determine a recommended phase II dose (RP2D). Secondary endpoints are cellular kinetics, overall response rate by investigator assessment, duration of response, overall survival and overall safety. **Results:** As of Dec 17th, 2024, a total of 10 eligible pts received Ori-C101 infusion at 3 dose levels (DLs). All pts had BCLC stage B or C, with 20% (2/10) had extrahepatic metastasis. The median number of prior lines of therapy was 4.5 (range 2-9), 100% pts received immune checkpoint inhibitors and tyrosine kinase inhibitors. All pts were evaluable for safety. All adverse events were reported regardless of study drug relationship. Of 10 pts evaluable for safety, the most common ≥ grade (G) 3 AEs were lymphocyte count decreased (100%), neutrophil count decreased (60.0%), blood fibrinogen decreased (40.0%), transaminases increased (40.0%), platelet count decreased (20.0%), blood bilirubin increased (20.0%). CRS was observed in 10 (100%) pts with 3 (30.0%) ≥ G3 CRS. No ICANS was observed. One pt developed DLT event due to CRS and secondary disseminated intravascular coagulation. 9 pts were evaluable for efficacy per RECIST 1.1. While 6 pts (66%) achieved disease control at DL2 or higher, all pts at the DL3 achieved objective response. Particularly, one pt who achieved CR showed encouraging durability and no signs of relapse at 9 months follow up evaluation, and follow up is ongoing. **Conclusions:** These preliminary data showed Ori-C101 has manageable safety profile and exciting efficacy with encouraging sign of good durability. Currently, more pts have been enrolled at dose expansion to confirm the DLs of RP2D. More information will be presented at coming ASCO conference. Clinical trial information: NCT05652920. Research Sponsor: None.

Modifiable risk-factors, genetic characteristics, and survival in early-onset cholangiocarcinoma.

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Background: Cholangiocarcinoma (CC) is a rare disease with an increasing incidence among younger adults, which is poorly understood. Genomic profiling of tumors is both prognostic and predictive of benefit for targeted therapies. We investigated if there are clinical and molecular differences between younger vs older patients with CC. **Methods:** We collected TEMPUS genetic data via retrospective chart review from tumors in young vs old patients seen at our institution, defined as ≤ 50 vs > 50 years of age at time of diagnosis. We included patients diagnosed with CC between January 2008 and July 2024 with available clinical follow up and TEMPUS genetic sequencing data. We collected mutation data on the following actionable genes: FGFR2, IDH1/2, BRCA1, BRCA2, BRAF, ATM, ERBB2/3, and KRAS. Patient characteristics and gene expression variables were compared using Chi-square, Fisher's exact and Wilcoxon rank-sum tests. Kaplan-Meier, log rank tests and a multivariable Cox model were used for survival analysis. This study was IRB exempt. **Results:** We included 410 patients, 84 in the young group with median age at diagnosis of 40.8 years, and 326 in the old group with median age 68.5 years. 91.5% of patients were white. There was no difference in BMI between groups, however the older group had higher rates of hypertension (15.5% vs 57.7%), hyperlipidemia (6.0% vs 49.7%), cardiovascular disease (1.2% vs 20.6%), and type 2 diabetes (6.0% vs 21.5%), (all $p < 0.01$). Primary sclerosing cholangitis was more common in the young group (26.2% vs 4.3%, $p < 0.01$). ECOG status of 0 at first treatment was seen in 65.3% of young vs 52.5% of old patients ($p = 0.02$). FGFR2 alterations were more common in the young group (17.9% vs 8.0%, $p < 0.01$), while ATM mutations were more common in old vs young (5.5% vs 0%, $p = 0.03$). There was no age difference seen for the other genetic alterations. Mean tumor mutational burden was higher in the old group (4.1 vs 3.8 mut/mb, $p = 0.01$). MSI-high was found in 2% of cases with no difference between groups. There was no significant difference in overall survival between age groups. There was a numeric difference in overall survival in stage IV patients, though not statistically significant (17.8 months vs. 16.3 months, $p = 0.08$). In a multivariable Cox analysis, female sex, earlier stage at diagnosis and clinical trial enrollment were associated with favorable prognostics. **Conclusions:** Our data highlight relatively low rates of comorbidities associated with metabolic dysfunction in younger adults with CC, suggesting alternative factors are likely to explain the increasing incidence of early-onset disease. FGRFR2 is a more common pathogenic alteration among the young and could inform targeted therapies. Younger patients with CC may not have improved survival outcomes compared to their older counterparts. This underscores the aggressive nature of CC and the need for more effective therapies to improve outcomes. Research Sponsor: None.

Real world efficacy and safety of ivosidenib in US veterans with IDH1 mutated cholangiocarcinoma.

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Background: IDH1 mutations occur in 13% of patients with intrahepatic cholangiocarcinoma. Ivosidenib is FDA approved for the treatment of advanced, previously treated, IDH1-mutated cholangiocarcinoma. In the ClarIDHy trial, ivosidenib led to an objective response rate of 2%, stable disease rate of 51%, median progression-free survival (PFS) of 2.7 months, and median overall survival (OS) of 10.3 months. Treatment-emergent adverse events resulted in study drug discontinuation in 7% of patients. Data on the real-world efficacy and safety of ivosidenib in cholangiocarcinoma remains limited. **Methods:** Patients with IDH1-mutated cholangiocarcinoma who were prescribed ivosidenib before December 1, 2024, were retrospectively identified from the national Veterans Affairs (VA) Corporate Data Warehouse. Demographic, clinical, and molecular data were abstracted from the National Precision Oncology database and electronic medical records. Response was assessed based on provider notes and radiology reports. Survival was assessed by the Kaplan-Meier method, and covariates evaluated by the Cox proportional hazards model. **Results:** Of 1094 veterans with cholangiocarcinoma who underwent molecular testing, 82 (7.5%) had an IDH1 mutation. 33 (40%) patients received ivosidenib at 27 VA medical centers. The median age was 74 years (range 46–82). 2 patients (6%) had a partial response (PR), 10 (30%) had stable disease (SD), 19 (58%) had progressive disease, and 2 were not assessed. 20 patients (60%) had received one and 5 patients (15%) received two prior lines of therapy. Of the 8 patients (24%) who received first-line ivosidenib, 2 (25%) had a PR and 3 (38%) had SD. Most patients (94%) started ivosidenib at the labeled dose (500 mg daily). Two patients who started ivosidenib at reduced dose (250 mg daily) had PR and SD as their best response. The median PFS from start of ivosidenib was 4.0 months, and the median OS was 10.5 months. In a multivariable analysis, PFS and OS were not significantly associated with age, line of therapy, IDH1 variant allele frequency, or IDH1 mutation (17 IDH1 R132C vs. 8 other). Patients with IDH1-mutated, advanced cholangiocarcinoma treated with ivosidenib had a median OS of 25.3 months from diagnosis, compared to 8.7 months for patients who did not receive ivosidenib. Toxicities leading to dose reduction, interruption, or discontinuation of ivosidenib occurred in 3 patients (9%). **Conclusions:** In this real-world cohort, patients with IDH1-mutated advanced cholangiocarcinoma treated with ivosidenib had similar response rate, PFS, and OS compared to ClarIDHy. Toxicities leading to dose reduction, interruption, or discontinuation were rare. The only two partial responses were observed in the first-line setting, including one with a reduced starting dose. This suggests that frontline ivosidenib may be a reasonable alternative for patients with advanced cholangiocarcinoma. Research Sponsor: None.

HAIC plus TAE combined with tislelizumab and surufatinib in unresectable intrahepatic cholangiocarcinoma: The REACH-01 trial.

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Background: REACH-01 (NCT06239532) is a single-arm, open label, prospective trial, aiming to evaluate the safety and preliminary effectiveness of hepatic artery infusion chemotherapy (HAIC) plus transcatheter arterial embolization (TAE) combined with tislelizumab and surufatinib as first-line therapy for unresectable intrahepatic cholangiocarcinoma (iCCA). **Methods:** Twenty-eight patients with pathologically confirmed iCCA received TAE with undrugged microspheres and hepatic arterial infusion of oxaliplatin (85 mg/m^2) and raltitrexed (3 mg/m^2) at an interval of at least 3 weeks along with intravenous tislelizumab (200 mg) Q3W and oral surufatinib (150 - 250 mg) once daily. The primary endpoint was the objective response rate (ORR). Secondary outcomes included progression-free survival (PFS), conversion to surgical resection rate, overall survival (OS), 1-year OS rate, disease control rate (DCR), and incidence of adverse events. **Results:** As of December 18, 2024, the median follow-up time was 9.33 months, 15 patients achieved partial response and the ORR was 57.69 % per RECIST v1.1 criteria. The conversion to surgical resection rate was 15.38 %. The DCR was 80.77 %. Secondary endpoints of progression-free survival, overall survival and 1-year OS rate were not mature at the time of the analysis. Further, treatment related adverse effects (TRAEs) of any grade occurred in 28 patients. Manageable grade 3 adverse events (AEs) occurred in 32.14% of patients, commonly elevated alanine aminotransferase (7.14%), anorexia (7.14%), and hypokalemia (7.14%). **Conclusions:** HAIC plus TAE combined with tislelizumab and surufatinib are safe and promising first-line treatment selection for unresectable iCCA. Clinical trial information: NCT06239532. Research Sponsor: Key Research and Development Program of Shandong Province; 2021CXGC011105; BeiGene Co. Ltd.

Efficacy and safety of regorafenib combination with PD-1 inhibitors vs. regorafenib monotherapy in second-line treatment for patients with unresectable hepatocellular carcinoma after failure of different first-line treatments: A multicenter retrospective real-world study.

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Background: Regorafenib is the first oral targeted drug as a second-line agent in patients with unresectable hepatocellular carcinoma (HCC) who progressed on sorafenib treatment.There is a lack of data to validate the second-line therapy after progression of targeted-immune combination therapy. Our aim was to investigate the efficacy and safety of regorafenib alone or in combination with a programmed death-1 (PD-1) inhibitor in second-line treatment for patients who have failed tyrosine kinase inhibitor (TKI) in combination with PD-1 or TKI monotherapy, respectively. **Methods:** A total of 288 patients were enrolled in this multicenter, retrospective study. These patients received regorafenib with or without PD-1 inhibitor (Sintilimab/Camrelizumab/Pembrolizumab) as second-line therapy after failure of TKI (sorafenib/lenvatinib) or such TKIs combined with PD-1 inhibitor (Sintilimab/Camrelizumab/Pembrolizumab). The primary study endpoint was the evaluation of overall survival (OS), while secondary study endpoints were progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), and treatment safety. **Results:** In the first line treatment, 126 patients received TKI and 162 patients received TKI plus PD-1. In the TKI cohort, the Reg-PD-1 group exhibited markedly higher ORR (29.69% vs 4.84%; p<0.001) and DCR (89.06% vs 67.74%; p=0.004), as well as longer median PFS (10.5 vs 4.7 months; p<0.001) and median OS (18.9 vs 14.0 months; p=0.03) compared to the Reg monotherapy group.There was no significant difference in PFS, OS, ORR, and DCR between the two groups in the TKI plus PD-1 cohort.The incidence of AEs was higher in the Reg-PD-1 group compared to the Reg group (81.25 % vs 58.06%; p=0.005) in the TKI cohort. And Reg-PD-1 group was comparable to Reg group (76.70% vs 66.10%; p=0.144) in the TKI Plus PD-1 cohort. **Conclusions:** Regorafenib plus PD-1 may enhance efficacy in uHCC patients who failed first-line TKI therapy. However, in patients who have progressed after first-line TKI plus PD-1 therapy, using regorafenib alone or in combination with PD-1 in second-line therapy does not show a significant difference in efficacy.These findings have significant implications for the selection of second-line treatment strategies for HCC patients, indicating that the combination of regorafenib and PD-1 might not provide additional benefits in certain patient subgroups. Research Sponsor: None.

Outcomes in the two cohorts.

	TKI			TKI plus PD-1		
Outcomes	Reg (n=62)	Reg-PD-1 (n=64)	P value	Reg (n=59)	Reg-PD-1 (n=103)	P value
CR	2	3	-	3	2	-
PR	1	16	-	6	21	-
SD	39	38	-	35	62	-
PD	20	7	-	15	18	-
ORR	4.84%	29.69%	< 0.001	15.25%	22.33%	0.276
DCR	67.74%	89.06%	0.004	74.58%	82.52%	0.227
PFS(m)	4.7	10.5	< 0.001	6.3	9.2	0.062
OS(m)	14.0	18.9	0.03	13.2	16.2	0.13

4089 Poster Session

Characterization of CLDN18 expression in a Western biliary tract cancer population.

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Background: Patients with advanced biliary tract cancer (BTC) have poor survival despite recent advances in chemoimmunotherapy. Claudin 18 (CLDN18) directed therapy has shown benefit in combination with FOLFOX or CAPOX in gastric cancer and may also have therapeutic utility in advanced BTC. However, there are limited data on CLDN18 RNA and protein expression in BTC, especially in Western populations. **Methods:** Exome-capture based RNA sequencing was performed on BTC tissue samples through the MI-ONCOSEQ study at the University of Michigan. Fragments per Kilobase of transcript per Million mapped reads (FPKM) was used to normalize raw read counts. Immunohistochemical staining was completed on a BTC tissue microarray (n = 28), and Western blotting was done on human BTC cell lines (SNU-1079, RBE, and SSP-25) using CLDN18 recombinant rabbit monoclonal antibody (34H14L15, Invitrogen). Statistical significance was defined as $p < 0.05$. **Results:** We identified transcriptomic data from 148 consecutive BTC cases with median age 61 (range 17-81) years and 75 (50.7%) were female. Of these patients, 45 (30.4%) expressed CLDN18 mRNA with FPKM > 1. A lower proportion of intrahepatic cholangiocarcinoma (CCA) patients (n = 23/110; 20.9%) expressed CLDN18 mRNA relative to extrahepatic CCA (n = 13/25; 54.2%) and gallbladder cancer (n = 8/11; 72.7%) ($p < 0.006$). CLDN18 mRNA expression was not associated with stage at diagnosis, but was higher in metastatic versus primary sites (35.6 vs 16.1%, $p < 0.05$). Overall survival was not associated with CLDN18 gene expression in univariate analysis (hazard ratio 1.02, $p > 0.9$). CLDN18 protein expression was observed in 8/28 (28.6%) patients using a cutoff defined in prior gastric cancer clinical trials (2+ to 3+ staining intensity in $\geq 75\%$ of tumor cells). In human BTC cell lines, SSP-25 expressed CLDN18, but the SNU-1079 and RBE lines did not. **Conclusions:** CLDN18 is expressed in a modest subset of Western patients with advanced BTC and CLDN18-directed therapy may be effective in this disease, particularly in ECC and gallbladder cancer given their higher frequency of expression. CLDN18 positive human BTC cell lines represent a promising preclinical model system for further investigation of this therapeutic strategy. Research Sponsor: National Cancer Institute; 5T32CA009357-42; Rogel Cancer Center.

TACE-HAIC combined with donafenib and immune checkpoint inhibitors for BCLC stage C HCC patients (THEME study): A retrospective IPTW adjusted cohort study.

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Background: Transarterial chemoembolization (TACE) combined with hepatic arterial infusion chemotherapy (HAIC) has demonstrated superior objective response rate (ORR) and progression-free survival (PFS) compared to TACE alone, particularly in patients with unresectable hepatocellular carcinoma (uHCC) with portal vein tumor thrombosis (PVTT), as shown in previous studies. Additionally, Donafenib exhibited significant survival benefits and better safety profiles compared to Sorafenib in a Phase III clinical trial. We aimed to retrospectively compare the efficacy and safety of TACE-HAIC combined with Donafenib and immune checkpoint inhibitors (Quadruple Therapy Group) versus the standardized targeted therapy (TKIs or bevacizumab) plus immune checkpoint inhibitors (Targeted-Immunotherapy Group) in patients with BCLC stage C hepatocellular carcinoma (HCC). **Methods:** We conducted a retrospective analysis of patients with BCLC stage C hepatocellular carcinoma (HCC) who received quadruple therapy or targeted-immunotherapy at the Harbin Medical University Cancer Hospital between September 2019 and October 2024. To minimize baseline imbalances between the groups, we applied stabilized inverse probability of treatment weighting (sIPTW) methods. **Results:** A total of 195 patients were included in the study, of whom 125 were assigned to the Quadruple Therapy Group and 70 to the Targeted-Immunotherapy Group. Within the Targeted-Immunotherapy Group, 44 patients received TKIs combined with immune checkpoint inhibitors, while 26 patients received bevacizumab combined with immune checkpoint inhibitors. After applying sIPTW to balance the baseline characteristics between the two groups, patients in the Quadruple Therapy Group demonstrated a significantly higher median overall survival (OS) compared with the Targeted-Immunotherapy Group(29.4 months [95% CI: 23.9—NA] vs 18.0 months [14.7—31.8]; P = 0.045). Additionally, the median progression-free survival (PFS) assessed by the modified Response Evaluation Criteria in Solid Tumors (mRECIST) was longer in the Quadruple Therapy Group(16.4 months [95% CI: 12.7—NA] vs 10.0 months [3.3—31.8]; P = 0.013). The objective response rate (ORR) evaluated according to mRECIST was also higher in the Quadruple Therapy Group(68.4% vs 28.2%, $P < 0.001$).The incidence of any adverse events in the Quadruple Therapy Group was 95.2%, compared with 97.1% in the Targeted-Immunotherapy Group.Among these the incidence of grade ≥ 3 adverse events was 40.8% in the Quadruple Therapy Group and 38.6% in the Targeted-Immunotherapy Group. **Conclusions:** Compared with Targeted-Immunotherapy Group, patients with BCLC stage C HCC treated with TACE-HAIC combined with Donafenib and immune checkpoint inhibitors therapy demonstrated superior efficacy and acceptable safety. Research Sponsor: None.

Multimodal evaluation of metabolic dysfunction–associated steatotic liver disease (MASLD)–related biliary tract cancer (BTC) and immunotherapy outcomes.

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Background: Rising incidence of BTC, particularly intrahepatic cholangiocarcinoma (iCCA), may be linked to increasing incidence of obesity, MASLD and type 2 diabetes mellitus (T2DM). Immunotherapy with immune checkpoint inhibitors (ICIs) has modestly extended survival in biliary tract cancer. However, the prevalence of MASLD in BTC, its immune microenvironment (TME) and outcome of MASLD-BTC with ICIs are unknown. **Methods:** Retrospective analysis of BTC patients (pts) treated with ICI between 5/2021-5/2024 with durvalumab, cisplatin, and gemcitabine. We used American Association for Liver Diseases (AASLD) criteria for MASLD: 1) metabolic dysfunction and 2) steatosis on imaging or biopsy. We calculated liver proton-density fat fraction (PDFF) in pre-treatment non-contrast CT scans (PDFF estimate 5% labelled as steatosis). We examined the statistical association between BMI and both tumor genotype and gene expression patterns using data from institutional genomic platforms (MAPP2 and RTI). **Results:** 179 BTC pts (65% of whom were iCCA) treated with durvalumab, cisplatin, and gemcitabine, 103 (57.5%) met AASLD MASLD criteria. In evaluable pts, the median overall survival (OS) was 18.4 months, and median follow-up time was 16.7 months. Non-MASLD pts had a median OS of 23.0 months (95% CI: 16.2, NA) versus 16.7 months (95% CI: 12.4, 21.2) with MASLD (p = .056). T2DM was associated with a worse OS (10.6 versus 21.2 months, p = .004). Multivariable cox model for OS demonstrated a hazard ratio (HR) of 1.45 (95% CI: 0.87, 2.4; p = .1564) for MASLD and 1.61 (95% CI: .99, 2.65; p = .0575) for T2DM. The median progression-free survival (PFS) was 8.5 months. MASLD BTC had a median PFS of 8.2 months (95% CI: 5.7, 10.1) versus 9.2 months (95% CI: 6.9, 16.2) without MASLD (p = .459). BTC pts with T2DM had median PFS of 5.8 months vs 13.0 months without T2DM (p = .001). Multivariable cox model for PFS had HR of 1.7 (95% CI: 1.1, 2.6; p = .014) for T2DM. Within our institutional database (n = 919), we observed depletion of *KRAS* (p = .008) and *STK11* (p = .02) mutations in BTC pts with high BMI. RNA-seq (n = 77) suggests that elevated BMI was associated with low expression of pan-immune and epithelial-to-mesenchymal transition and increased expression of oxidative phosphorylation signatures. **Conclusions:** BTC is commonly associated with MASLD and may correlate with reduced OS and PFS with ICI, particularly in T2DM pts. Our findings suggest a distinct immunogenomic signature in MASLD-BTC and highlight the importance of further investigating the TME in this population. Research Sponsor: None.

Phase 1 expansion study of FF-10832 (liposomal gemcitabine) antitumor activity in patients with advanced biliary carcinomas.

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Background: FF-10832 has demonstrated improved pre-clinical anti-tumor activity compared to gemcitabine (GEM). Associated factors may include its prolonged circulating half-life, tumor accumulation, and immune activation.The first in human dose finding trial of FF-10832 demonstrated a tolerable safety profile and anti-tumor activity in heavily pre-treated patients (pts) with solid tumors who progressed on prior gemcitabine. A biliary tract cancer (BTC) pt maintained a PR >60 weeks after progression on prior GEM based therapy. We subsequently enrolled an expansion cohort evaluating FF-10832 monotherapy in BTC and describe the results (NCT03440450). **Methods:** Pts ≥18 years with advanced BTC who had progressed on up to 3 lines of therapy were treated with FF-10832 40 mg/m^2 IV Day 1 Q 21 days until disease progression or unacceptable toxicity. Response was assessed by RECIST 1.1. Modulation of immune cells (flow cytometry/multiomics) and population PK were assessed. **Results:** 18 pts [12M/6F; median age 68 (34-79), ECOG PS 0 (3) PS 1 (15)] were treated; median # prior therapies, 2 (1-3); all had prior GEM and 16 had progressed on prior GEM. Pts received a median of 4 (1 - 22+) cycles with a median time on study of 10.4 (3.3 -77+) weeks. FF-10832 was well-tolerated. The most common drug-related AEs were nausea, pyrexia, and decreased appetite (39% each). No Gr 4 toxicity was observed; Gr 3 AEs in >1 pt included anemia (2) and muscular weakness (2). All AEs were successfully managed using standard therapies. Two pts withdrew and 1 pt died of cholangitic sepsis before 1st evaluation. Best overall response in 15 remaining pts was 2 PR, 8 SD, 4 PD and 1 NE. The median PFS and OS were 3.4 and 9.1 months, respectively. Both PRs had received prior GEM/platinum-based therapy: 1) a gallbladder adenocarcinoma pt achieved a 48% decrease in target lesions with FF-10832 by cycle 2, which was maintained through cycle 10; dose was reduced to 30 mg/m^2 at cycle 5 for Gr 3 muscle weakness, 2) a hilar cholangiocarcinoma pt achieved a PR by cycle 2,with complete resolution of target lesions before withdrawing. Four additional pts maintained SD ≥ 6 cycles, with 2 continuing on therapy after 9 and 26 cycles. PK was similar to that previously reported (terminal $t_{1/2,}$ 30 hours), with similar log decreases observed in Ki67+ regulatory T cells and increases observed in CD8+ cells, indicative of anti-tumor immune activation. **Conclusions:** FF-10832 is well-tolerated and has anti-tumor activity in pts with advanced BTC who progressed on prior GEM. Although preliminary, these results of a single agent therapy compare favorably to those reported for 2nd line combination therapies. This warrants further investigation of FF-10832 efficacy and safety in BTC patients. Clinical trial information: NCT03440450. Research Sponsor: FUJIFILM Pharmaceuticals USA Inc.

SHR-8068 plus adebrelimab and bevacizumab for advanced hepatocellular carcinoma (aHCC): A phase 1b/2 study.

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Background: Combination of an anti-PD-1/L1 antibody with an anti-angiogenic agent is currently the preferred 1L treatment for aHCC. Addition of a CTLA-4 inhibitor may further improve anti-tumor activity, with complementary immunostimulatory effects from CTLA-4 and PD-1/L1 blockade. We conducted a multicenter, open-label, phase 1b/2 trial (NCT05444088) to assess SHR-8068, a novel anti-CTLA-4 monoclonal antibody (mAb), combined with adebrelimab (A, anti-PD-L1 mAb) and bevacizumab (B) in patients (pts) with aHCC. **Methods:** Pts with or without prior treatment were enrolled (phase 1b: failed or refused standard therapy; phase 2: ≤1L systemic therapy, no immunotherapy [IO]). SHR-8068 was evaluated in 2 dosing regimens with AB: 1 mg/kg Q6W (Combo 1) or 4 mg/kg priming dose (Combo 2). An additional cohort evaluated AB alone (Combo 3). A was dosed at 20 mg/kg Q3W and B at 15 mg/kg Q3W for all regimens. **Results:** As of Oct 31, 2024, a total of 27, 53 and 21 pts received Combo 1, 2, and 3, respectively, across 2 study phases (overall: IO naïve, 97.0%; prior anti-angiogenic therapy, 32.7%); median follow-up was 16.7, 11.1 and 11.3 mo, respectively. In pts treated with Combo 2, the objective response rate (ORR) was 47.2% (25/53; 95% CI 33.3%–61.4%), with a median duration of response (DoR) of 12.7 mo (95% CI 5.8–NR). The median progression-free survival (PFS) was 8.7 mo (95% CI 5.5–11.6); median overall survival (OS) was not reached, with a 12-mo OS rate of 76.0% (95% CI 59.3%–86.6%). Numerically improved ORR and survival outcomes were seen with Combo 2 *vs* Combo 1 and 3 (Table 1). Overall, grade ≥3 treatment-related adverse events (TRAEs) occurred in 55.6%, 41.5% and 42.9% of pts with Combo 1, 2 and 3. The most common grade ≥3 TRAEs (incidence ≥10% for any Combo) were decreased platelet count (22.2%, 5.7%, and 4.8% for Combo 1, 2, and 3) and hypertension (18.5%, 7.5%, and 9.5%, respectively). TRAE led to discontinuation of any study agent in 11.1%, 1.9% and 9.5% of pts, respectively. There was 1 treatment-related death (Combo 3). **Conclusions:** SHR-8068 combined with adebrelimab and bevacizumab showed promising efficacy and manageable safety in aHCC. A more favorable benefit-risk profile was observed for SHR-8068 given as a priming dose. A phase 3 trial (NCT06618664) is currently underway to further assess the combination as 1L treatment for aHCC. Clinical trial information: NCT05444088. Research Sponsor: Jiangsu Hengrui Pharmaceuticals, Co., Ltd.

Efficacy outcomes.

	Combo 1 (n=27)	Combo 2 (n=53)	Combo 3 (n=21)
ORR, % (95% CI)	29.6 (13.8–50.2)	47.2 (33.3–61.4)	19.0 (5.5–41.9)
Median DoR*, mo (95% CI)	NR (9.4–NR)	12.7 (5.8–NR)	NR (7.0–NR)
9-mo DoR rate*, % (95% CI)	100.0 (NR–NR)	69.8 (41.7–86.3)	66.7 (5.4–94.5)
DCR, % (95% CI)	77.8 (57.7–91.4)	77.4 (63.8–87.7)	81.0 (58.1–94.6)
Median PFS*, mo (95% CI)	6.9 (2.7–NR)	8.7 (5.5–11.6)	6.7 (2.8–9.5)
12-mo OS rate*, % (95% CI)	70.4 (49.4–83.9)	76.0 (59.3–86.6)	70.8 (46.2–85.7)

Tumor response was assessed by investigator per RECIST v1.1.
*Kaplan-Meier method. NR, not reached.

Hepatic arterial infusion chemotherapy combined with donafenib and tislelizumab versus transcatheter chemoembolization alone for hepatocellular carcinoma: A propensity score matching study.

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Background: Although tyrosine kinase inhibitors combined with PD-1/L1 inhibitors have been established as first-line treatment for advanced hepatocellular carcinoma (HCC), the survival benefit remains unsatisfactory. Hepatic arterial infusion chemotherapy (HAIC) has emerged as an effective therapy to improve the prognosis of HCC patients. This study aimed to investigate the efficacy and safety of HAIC combined with donafenib and tislelizumab in HCC. **Methods:** 421 patients diagnosed as HCC and treated in Sun Yat-sen University Cancer Center from January 2017 to December 2024 were enrolled in this retrospective study, included 151 patients received FOLFOX-HAIC combined with donafenib and tislelizumab (DT-HAIC) and 270 received transcatheter chemoembolization (TACE) alone. To avoid the selection bias and balance covariates, we conducted propensity score matching (PSM). The primary outcomes are progression-free survival (PFS) and overall survival (OS); the secondary outcomes include objective response rate (ORR), disease control rate (DCR) and safety. Tumor response was evaluated per RECIST v1.1. **Results:** PSM resulted in 151 matched pairs with comparable baseline characteristics between the DT-HAIC and TACE cohorts. Compared with the TACE cohort, Patients receiving DT-HAIC exhibited significantly better median PFS (10.3 vs 4.9 months, $P < 0.01$) and median OS (not reached vs 10.9 months, $P < 0.01$). The ORR and DCR were significantly higher in the DT-HAIC cohort than in the TACE cohort (ORR: 33.8% vs 11.3%, $P < 0.01$; DCR: 77.9% vs 65.3%, $P = 0.03$). There was no treatment-related death. Serious adverse events were similar between the two groups, except for alanine aminotransferase (ALT), aspartate aminotransferase (AST), platelet count, abdominal pain and allergic reaction. In the TACE cohort, the occurrence of Grade 3-4 elevations in ALT (11.3% vs 21.9%, $P = 0.02$) and AST (21.2% vs 36.4%, $P < 0.01$), as well as abdominal pain (2.6% vs 16.6%, $P < 0.01$), was more prevalent. In contrast, the DT-HAIC cohort exhibited a higher incidence of Grade 3-4 thrombocytopenia (11.3% vs 1.3%, $P < 0.01$) and allergic reactions (4.6% vs 0, $P = 0.02$). **Conclusions:** DT-HAIC significantly improved PFS, OS, ORR, and DCR compared with TACE alone, with manageable adverse events, suggesting that the combination of HAIC with donafenib and tislelizumab may be a promising treatment option for HCC patients. Research Sponsor: None.

	DT-HAIC (n=151)	TACE (n=151)	P Value
mPFS	10.3m	4.9m	P<0.01
mOS	Not reached	10.9m	P<0.01
ORR	33.8%	11.3%	P<0.01
DCR	77.9%	65.3%	P=0.03

LEAP-002 long-term follow-up: Lenvatinib plus pembrolizumab versus lenvatinib plus placebo for advanced hepatocellular carcinoma.

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Background: LEAP-002 was a randomized, double-blind, phase 3 study (NCT03713593) that was conducted to evaluate the efficacy and safety of first-line lenvatinib plus pembrolizumab versus lenvatinib plus placebo in participants with advanced hepatocellular carcinoma (HCC). The study did not meet its primary end points of OS at final analysis and PFS at interim analysis. After a median study follow-up of 43.6 months, OS, PFS, and ORR remained consistent with the primary efficacy analysis (OS: HR, 0.84 [95% CI, 0.71-0.98]; PFS: HR, 0.81 [95% CI, 0.69-0.95]; ORR, 26.3% vs 17.5%); no new safety signals were observed. Here, we present results based on an additional 15 months of follow-up. **Methods:** Eligible participants with advanced HCC were randomly assigned 1:1 to receive lenvatinib (8 mg/day if bodyweight [BW] $<$ 60 kg; 12 mg/day if BW $\geq$60 kg) plus pembrolizumab (200 mg IV Q3W) or lenvatinib plus placebo. Dual primary end points were OS and PFS (per RECIST v1.1 by BICR). Secondary end points included ORR and DOR, both per RECIST v1.1 by BICR, and safety. The database cutoff was September 24, 2024. **Results:** 794 participants were randomly assigned to receive lenvatinib plus pembrolizumab (n = 395) or lenvatinib plus placebo (n = 399). Median study follow-up was 59.2 mo (range, 52.9-68.3). The HR for OS was 0.80 (95% CI, 0.69-0.94; median, 21.1 months with lenvatinib plus pembrolizumab vs 19.0 months with lenvatinib plus placebo). 60-month OS rates were 19.7% with lenvatinib plus pembrolizumab versus 10.7% with lenvatinib plus placebo. Grade 3-5 treatment-related adverse event (AE) rates were 62.8% with lenvatinib plus pembrolizumab and 58.0% with lenvatinib plus placebo. No additional deaths due to treatment-related AEs were reported since the final analysis (database cutoff, June 21, 2022). Overall, 47.3% of participants treated with lenvatinib plus pembrolizumab versus 56.1% of participants treated with lenvatinib plus placebo received subsequent systemic therapy (TKI/VEGF, 38.5% vs 42.6%; immunotherapy, 17.2% vs 26.8%; chemotherapy, 5.3% vs 4.0%); 21.5% versus 25.6% received subsequent liver-directed therapy (locoregional therapy, 20.0% vs 23.8%; surgery, 2.8% vs 2.8%). **Conclusions:** The LEAP-002 study did not meet its primary end points; however, with a long-term follow-up of 5 years, almost twice as many participants randomly assigned to receive lenvatinib plus pembrolizumab versus lenvatinib plus placebo were alive at database cutoff; no new safety signals were observed. Clinical trial information: NCT03713593. Research Sponsor: Eisai, Inc., Nutley, NJ, USA, and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Membrane-specific HER2 expression by artificial intelligence-based quantitative scoring for prediction of efficacy of trastuzumab deruxtecan in biliary tract cancer (HERB trial): Exploratory analysis of a multicenter, single arm, phase II trial.

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Background: Trastuzumab deruxtecan (T-DXd) showed promising results in patients with HER2-positive biliary tract cancer (BTC). With T-DXd's expanding indication into HER2-low cancers, quantitative Artificial Intelligence (AI)-based scoring of HER2 expression at the cellular level becomes increasingly important. This study investigated whether the intensity and subcellular pattern of HER2 staining would correlate with response to T-DXd. **Methods:** HER2 immunohistochemistry (IHC) whole slide images from the phase II HERB trial were analyzed. These participants had unresectable or recurrent BTC refractory or intolerant to gemcitabine-containing regimen and received T-DXd based on confirmed HER2-positive or low status. Lunit SCOPE universal IHC, a deep learning based IHC analyzer, was used to provide cell level classes (AI-H0, H1+, H2+, H3+) and continuous scoring of HER2 staining intensities of subcellular compartments (membrane, cytoplasm and nucleus) for each tumor cell. Membrane specificity was calculated for each cell as the ratio of membrane intensity to the sum of all three subcellular compartments. **Results:** The 29 patients analyzed showed continuous improvement in response rates with an increasing proportion of AI-H3+ cells. The ORR was 37.5%, 42.9% and 50.0% for patients with more than 10%, 25%, and 50% of tumor cells classified as AI-H3+, respectively. The HER2 intense cohort (n=4), defined by tumors with over 50% of tumor cells classified as AI-H3+, had a significantly better PFS (HR 0.15, $p<0.05$) and OS (HR 0.10, $p<0.05$) compared to the rest of the treatment group. The high membrane specificity group defined by ≥80% of tumor cells with membrane specificity ≥0.4 (N=6) had a confirmed ORR of 50%. These patients also demonstrated significantly longer PFS (HR 0.30, $p<0.05$) and OS (HR 0.27, $p<0.05$). The six cases identified by membrane specificity included all four cases of the HER2 intense cohort and two more cases, showing improved sensitivity in identifying likely responders. **Conclusions:** AI based quantification of HER2 intensity and membrane specificity was predictive of therapeutic response to T-DXd in HER2 expressing BTC. Membrane specificity analysis was more sensitive in identifying exceptional responders compared to intensity alone.
Research Sponsor: None.

Confirmed response and survival based on AI defined biomarkers.

	By AI-H3+ proportion		By AI-MB specific cell proportion	
	< 50%	≥ 50%	< 80%	≥ 80%
Sample size	25	4	23	6
ORR, %	28.0	50.0	26.1	50.0
mPFS	4.21 (2.83-4.40)	11.04 (5.68-12.91)	4.21 (2.83-4.40)	11.04 (1.45-12.91)
HR (95% CI, p-value)	REF	0.15 (0.03-0.67, <0.05)	REF	0.30 (0.10-0.92, <0.05)
mOS	7.00 (4.37-8.94)	NR (5.68-NR)	7.00 (4.27-8.94)	NR (9.63-NR)
HR (95% CI, p-value)	REF	0.10 (0.01-0.79, <0.05)	REF	0.27 (0.08-0.93, <0.05)

A prospective, observational phase II clinical study evaluating hepatic artery infusion chemotherapy in combination with HLX10 and HLX04 as first-line treatment for patients with advanced hepatocellular carcinoma.

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Background: Advanced hepatocellular carcinoma (HCC) presents limited treatment options. Immunotherapy has emerged as an effective treatment, demonstrating encouraging outcomes and acceptable adverse reactions in advanced HCC. This study aims to assess the efficacy and safety of HLX10 (recombinant anti-PD-1 humanized monoclonal antibody) and HLX04 (recombinant anti-VEGF humanized monoclonal antibody), in combination with hepatic artery infusion chemotherapy (HAIC), as first-line treatment for advanced HCC. **Methods:** This prospective, observational, single-center Phase II trial enrolled untreated HCC patients with BCLC stage C. All patients received HLX10 (4.5 mg/kg, intravenous infusion, every 3 weeks) and HLX04 (15.0 mg/kg, intravenous infusion, every 3 weeks) on Day 1 of each treatment cycle, followed by HAIC with the FOLFOX regimen. HAIC was administered for a maximum of 8 cycles, while HLX10 and HLX04 were continued for up to 2 years, until death, disease progression, or intolerable toxicity occurred. The primary endpoint was the objective response rate (ORR), assessed by the investigator according to RECIST v1.1 criteria. Secondary endpoints included the disease control rate (DCR), progression-free survival (PFS), and safety. **Results:** Between August 2023 and September 2024, a total of 35 eligible patients were enrolled in the study. As of the data cut-off, 28 (80.0%) patients had received at least 3 cycles of treatment. Of the 35 patients, 32 underwent at least one assessment of treatment response, with the best outcomes as follows: 17 (53.1%) achieved partial remission (PR), and 12 (40.0%) had stable disease (SD). The ORR and DCR were 53.1% and 90.6%, respectively. Notably, among patients who had received at least 3 cycles of treatment, 17 patients achieved PR, resulting in an ORR of 63.0%. Moreover, 5 patients underwent successful hepatectomy after at least 3 cycles of treatment, and postoperative pathological evaluation revealed extensive tumor necrosis in the excised tissues. The median follow-up duration was 8.4 months, during which 6 (18.8%) patients experienced disease progression, yielding a one-year PFS rate of 70.5% (95% CI: 47.0%–85.0%). In terms of safety, 17 patients (48.6%) experienced at least one grade 3 or 4 adverse event (AE), with the most frequent being decreased lymphocyte count (20%). **Conclusions:** The combination of HLX10, HLX04, and HAIC as first-line treatment for advanced HCC has demonstrated promising efficacy, particularly in patients completing three or more cycles. The safety profile of this combination therapy was acceptable, with manageable AEs. Further investigation in larger trials is warranted. Clinical trial information: NCT06370065. Research Sponsor: None.

Cobolimab and dostarlimab in the first-line treatment of unresectable hepatoma: A multi-center, single arm, phase 2 trial.

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Background: TIM-3 is highly expressed in cancer and mediates T cell exhaustion/dysfunction that can be an important mechanism of immune escape. Cobolimab, an anti-TIM-3 monoclonal antibody, in combination with dostarlimab (a PD-1 inhibitor), has been shown to enhance T-cell activity in preclinical assessments. This study aimed to investigate the efficacy and safety of cobolimab and dostarlimab in the treatment of unresectable hepatocellular carcinoma (HCC). **Methods:** This is a multi-center, single-arm, phase II study. Eligible patients with unresectable hepatoma (Barcelona Clinic Liver Cancer Stage B or C) and Child Pugh A or B7 (limit 6) liver function received cobolimab 300mg and dostalimab 500mg every 3 weeks for up to 2 years. The primary endpoint was the objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors version1.1. Secondary endpoints were disease control rate (DCR) and duration of response (DoR), progression-free survival (PFS), overall survival (OS), and safety. **Results:** 40 patients were treated (mean age 67 years [range: 24–85]). The analysis presented here is for all 34 Child Pugh A patients. As of November 6, 2024, the median follow-up was 12.9 months. The ORR and DCR were 37.1% and 85.2% respectively (3.7% CR, 33.3% PR, 48.1% SD). The median PFS was 11.0 mo (95% CI: 4.6-17.4), and the median OS was 27.3 mo (95% CI: 21.1-33.5). The median DoR was 14.8 mo (95% CI: 9.4-20.2). Overall incidences of adverse events (AEs) of any grade was 97.1% and immune-related AEs (irAEs) of any grade was 64.7%. The most common irAEs of any grade were dermatologic (47.1%) and endocrine (14.7%). There were two patients (5.8%) who experienced mild elevations of AST and ALT. Grade ≥3 irAEs were observed in two patients (5.8%), which included decreased neutrophil count, hypophysitis, and hypothyroidism. There were no treatment-related discontinuations or deaths. **Conclusions:** Cobolimab plus dostarlimab yielded promising response rates and survival outcomes with acceptable safety as first-line treatment in patients with CP A, unresectable HCC. This represents a potential therapy regimen for this population. Clinical trial information: NCT03680508. Research Sponsor: GSK.

Sorafenib plus hepatic arterial infusion chemotherapy versus sorafenib plus transarterial chemoembolization in advanced hepatocellular carcinoma: An update on SHATA-001 study.

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Background: Although sorafenib plus transcatheter arterial chemoembolization (SoraTACE) has been widely applied for advanced hepatocellular carcinoma (HCC) in most Asian countries, sorafenib plus hepatic arteria infusion chemotherapy (SoraHAIC) may be a better alternative. Herein, we compared the efficacy and safety between the two groups in advanced HCC. Additionally, we validated a predictive model from our previous phase III trial (NCT02973685, cohort1). **Methods:** This phase III trial (NCT02856126) recruited participants with advanced HCC. Eligible participants were randomly assigned (2:1) to receive Sorafenib (400mg orally twice daily) plus HAIC per 3 weeks or TACE until disease progression or unacceptable toxicity. The Primary endpoint was overall survival (OS). Whole-exome sequencing (WES), RNA sequencing, and DNA methylation analysis of tumor biopsy samples were performed for predictive biomarker exploration (cohort 1) and validation (SHATA-001). **Results:** From August 2016 to October 2020, a total of 207 participants were allocated to receive SoraHAIC (n = 141) or SoraTACE (n = 66). The trial met the prespecified endpoints. SoraHAIC significantly prolonged OS compared to SoraTACE (median OS, 15.7 versus 11.2 months; $p < 0.001$). In the SoraTACE group, 56.7% of participants experienced grade 3 or 4 treatment-related adverse events, which were significantly higher than the SoraHAIC group (39.3%; $p < 0.023$). Severe adverse events were also more frequent in SoraTACE (15.7% vs 26.7%, $p = 0.07$). WES analysis found no ideal indicator in the mutational landscape for treatment outcome. We identified 1226 and 506 differentially methylated probes (DMPs) among the non-responsive specimens in the HAIC and TACE groups. Then we performed RNA-seq analysis. By comparing the transcriptome between the responsive and non-responsive groups, 685 and 600 differentially expressed genes (DEGs) were generated in the two treatment groups, respectively. In the HAIC group, pathways including leukocyte-mediated immunity and immune response-activating signaling pathway were enriched in the responders, while metabolic-related pathways including steroid metabolic process and alcohol biosynthetic process were enriched in the non-responders in the TACE group. Integrative analysis of DEGs and DMPs indicated phosphofructokinase (PFKM) could potentially stratify patients to HAIC or TACE as higher expression of PFKM was associated with favorable outcomes accepting TACE. Such performance could also be validated in this study as participants with elevated PFKM tended to benefit from SoraTACE. **Conclusions:** This trial demonstrated SoraHAIC significantly improved OS over SoraTACE in participants with advanced HCC. Participants with high PFKM expression benefited more from TACE. Clinical trial information: NCT02856126. Research Sponsor: None.

Survival outcomes for zanidatamab-hrii compared to chemotherapy in previously treated HER2-positive (IHC3+) biliary tract cancer (BTC): HERIZON-BTC-01 vs a real-world (RW) external control arm (ECA).

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Background: Zanidatamab-hrii, a bispecific HER2-directed antibody, received accelerated approval for adults with previously treated, unresectable or metastatic HER2-positive (IHC 3+) BTC based on results from the single-arm phase 2 HERIZON-BTC-01 trial. The results here compare survival outcomes with zanidatamab-hrii from HERIZON-BTC-01 vs a comparable RW cohort of patients who received second-line (2L) chemotherapy. **Methods:** HERIZON-BTC-01 (NCT04466891) evaluated zanidatamab-hrii (20 mg/kg IV every 2 weeks) in patients with HER2-amplified, unresectable locally advanced or metastatic BTC (gallbladder cancer [GBC], intra-/extra-hepatic cholangiocarcinoma [ICC/ECC]) who had received prior gemcitabine-containing therapy. HERIZON-BTC-01 patients with HER2 IHC3+ (n = 62) were included in this analysis. The US-based ECA was constructed using deidentified data from the Flatiron Health Electronic Health Record. Key inclusion criteria for the ECA included a diagnosis of GBC or ICC/ECC with initiation of 2L chemotherapy between 2011-2023, HER2 IHC3+ prior to 2L initiation, and 1L treatment with a gemcitabine-containing regimen. Patients with ECOG >1 or CNS metastases were excluded. Standardized mortality ratio (SMR) weighting was used to account for potential imbalance of key prognostic factors. Overall survival (OS) and progression-free survival (PFS) were evaluated using SMR-weighted Kaplan-Meier and Cox proportional hazards regression. **Results:** Among 290 RW patients initiating 2L treatment with HER2 testing, 12 met all eligibility criteria and were included in the ECA. The most common reason for exclusion was lack of HER2-positivity (n = 209). Median follow-up times were 16.1 (interquartile range [IQR]: 9.4, 19.9) and 4.7 (IQR: 2.6, 8.1) months for the zanidatamab-hrii and ECA arms, respectively. After weighting, baseline characteristics were similar across arms with standardized mean differences ≤ 0.2. The most common 2L chemotherapy regimen in the ECA was FOLFOX (n =6), followed by gemcitabine-based regimens (n = 3) and FOLFORI (n = 2). Compared with chemotherapy, zanidatamab-hrii resulted in longer median OS (18.07 vs 3.29 months; hazard ratio [HR]:0.29) and PFS (7.26 vs 2.30; HR: 0.47) (Table). The 6- and 12-month survival for zanidatamab-hrii patients were 90% and 65% (vs. 29% and 13% for the ECA), respectively. **Conclusions:** Among patients with previously-treated HER2-positive (IHC3+) BTC, zanidatamab-hrii resulted in longer survival, including a >14 month increase in median OS, vs ECA patients treated with chemotherapy. Research Sponsor: Jazz Pharmaceuticals.

	Zanidatamab-hrii (N=62)	ECA (N=12)
OS		
Median, mos	18.07	3.29
Survival % (95% CI)		
6 mos	90% (83%, 98%)	29% (11%, 75%)
12 mos	65% (54%, 78%)	13% (3%, 55%)
PFS		
Median, mos	7.26	2.30
Survival % (95% CI)		
6 mos	55% (44%, 69%)	14% (4%, 47%)
12 mos	32% (22%, 46%)	14% (4%, 47%)

Concordance analysis between tumor tissue HER2 status by immunohistochemistry (IHC) and in situ hybridization (ISH) and a translational analysis of plasma ctDNA in patients (pts) with biliary tract cancer (BTC): An exploratory analysis from the phase 2 HERIZON-BTC-01 trial.

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Background: HER2 is a target for precision oncology. HER2 protein overexpression and/or gene amplification is observed in a subset of pts with BTC. Zanidatamab (zani), a dual HER2-targeted bispecific antibody, received accelerated approval as a treatment for adults with previously treated, unresectable, or metastatic HER2-positive (IHC 3+) BTC based on the phase 2b HERIZON-BTC-01 trial. In this exploratory analysis, we evaluated concordance between tissue-based HER2 IHC and ISH in screened pts, and *HER2* gene amplification between tissue-based HER2 ISH and plasma ctDNA by NGS in zani-treated pts. **Methods:** In HERIZON-BTC-01 (NCT04466891) pts were screened for *HER2* gene-amplified tumors by ISH (VENTANA HER2 Dual ISH DNA Probe Cocktail assay) at a central laboratory. Pts with *HER2* gene amplification were prospectively assigned to cohorts based on centrally determined HER2 IHC score (Ventana PATHWAY [4B5] IHC assay); cohort 1: IHC 2+ or 3+; cohort 2: IHC 0 or 1+. HER2 status was assessed in a fresh biopsy or an archived sample per ASCO/CAP guidelines, with gastric cancer algorithm. Enrolled pts received zani 20 mg/kg IV Q2W in 28-day cycles. Plasma ctDNA samples were collected prior to the first cycle of zani (baseline) and on-treatment at cycle 2 day 28 for testing with NGS Guardant360 (Guardant Health). Guardant360 Molecular Response (MR) scores were calculated based on changes in plasma ctDNA levels from baseline. **Results:** Overall, 756 screened pts had central results for both HER2 IHC and ISH. Nearly all pts (94%) with HER2 IHC 3+ BTC had *HER2*-amplified tumors per ISH (Table). Among all 87 pts treated with zani across both cohorts, 48 samples from 25 pts were available for testing with NGS. The concordance between *HER2* gene amplification by ISH and ctDNA NGS was 59%. Co-mutations at baseline in plasma ctDNA occurring in > 10% of pts included KRAS (n = 1 [3%]), *HER2* S310F (n = 3 [9%]), and PIK3CA (n = 6 [18%]). Overall, 18/25 (72%) pts had a decrease in ctDNA levels from baseline at cycle 2 day 28; decreases > 90% were observed in pts with a best response of partial or stable disease. MR scores correlated with tumor response (ANOVA, P = 0.0189). **Conclusions:** In this analysis, there was a high concordance (94%) observed between tumor tissue HER2 IHC 3+ status and *HER2* gene amplification among pts screened in HERIZON-BTC-01. Exploratory translational analysis shows that treatment with zani after 2 cycles was associated with a decrease in plasma ctDNA levels in the majority of pts. Clinical trial information: NCT04466891. Research Sponsor: Jazz Pharmaceuticals.

HER2 IHC and ISH status among screened patients.

	ISH Status			
IHC Status	Amplified	Non-Amplified	Total	Amplification n/N (%)
0	12	330	342	12/342 (3.5)
1+	8	94	102	8/102 (7.8)
2+	34	167	201	34/201 (16.9)
3+	104	7	111	104/111 (93.7)
Total	158	598	756	158/756 (20.9)

The efficacy of atezolizumab plus bevacizumab for advanced hepatocellular carcinoma in relation to tumor-infiltrating lymphocytes: Histological assessment of CD8+ T cell spatial features as predictive biomarkers.

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Background: The combination of atezolizumab and bevacizumab (Atez/Bev) has improved prognosis in advanced hepatocellular carcinoma (HCC), though its therapeutic mechanisms remain unclear. While the tumor microenvironment (TME) holds promise for biomarker discovery, current studies rely on archived diagnostic samples. We aimed to elucidate molecular determinants of treatment efficacy and identify predictive biomarkers through comprehensive TME analysis of pre-treatment samples. **Methods:** We analyzed biopsy samples from 94 advanced HCC patients immediately before initiating Atez/Bev treatment using immunohistochemistry (IHC), RNA-sequencing, flow cytometry, and multiplexed imaging. Our analysis focused on spatial characteristics of CD8+ T cells and effector regulatory T (eTreg) cells, with longitudinal assessment of immune responses during treatment. **Results:** High programmed death-1 (PD-1) positivity in CD8+ T cells was significantly associated with favorable progression-free survival (PFS) (HR 0.24, 95% CI 0.11-0.52), while CD8+ T cell density showed no significant correlation (HR 1.12, 95% CI 0.64-1.95). Through multiplexed imaging analysis using PD-1 positivity as a key indicator, we identified two critical determinants of response: CD8+ T cells localizing within tumor parenchyma rather than fibrous stroma, and maintaining diffuse distribution throughout the tumor parenchyma. These features, assessable with routine hematoxylin and eosin and CD8 IHC staining, stratified patients into four prognostic groups ($p = 0.019$), with median PFS ranging from 14.3 months (both favorable features) to 3.5 months (neither feature). The PD-1 positivity in eTreg cells was not associated with prognosis (HR 0.75, 95% CI 0.34-1.62). Notably, bevacizumab counteracted the potential negative effects of programmed death-ligand 1 blockade by suppressing eTreg cell activation, as demonstrated through analysis of patients who discontinued bevacizumab and in vitro experiments showing reduced expression of eTreg activation markers. **Conclusions:** We demonstrate that routine histological assessment of CD8+ T cell localization and distribution patterns can predict Atez/Bev efficacy in advanced HCC. The identified synergistic mechanism of bevacizumab-mediated eTreg suppression provides a framework for future combination immunotherapy development.
Research Sponsor: CHUGAI PHARMACEUTICAL CO., LTD.

Radiomic analysis on pretreatment MRI to predict response to atezolizumab plus bevacizumab in advanced hepatocellular carcinoma: A multicenter study.

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Background: The combination of atezolizumab and bevacizumab is the standard treatment for advanced hepatocellular carcinoma approved in China and many other countries. However, the objective response rate of this combination treatment was around 30%. Consequently, identifying individuals with the potential to respond favorably prior to initiating therapy remains a pressing challenge. **Methods:** This multi-center retrospective study included advanced hepatocellular carcinoma patients who received atezolizumab plus bevacizumab as first-line therapy between December 2020 and February 2024. The training cohort consisted of eligible patients who have complete baseline, treatment and tumor evaluation records and MRI imaging data from Zhongshan Hospital, while eligible patients from other centers constituted the external validation cohort. A deep learning model based on nnU-Net was developed to automatically segment intrahepatic lesions. All segmentations were reviewed and revised by two radiologists. The radiomic features were extracted using PyRadiomics, then a radiomic feature-based model for predicting response to atezolizumab plus bevacizumab therapy was constructed using the Extreme Gradient Boosting Decision Tree (XGBoost) algorithm. Additionally, three radiologists evaluated 53 visually-assessed MRI features on MRI scans. Finally, the predictive performance of radiomic feature model, as well as the relationship between radiomic and MRI features, was assessed. **Results:** A total of 240 eligible patients were recruited from 14 centers in China, of which 161 and 79 were classified as training and validation cohorts, respectively. During a median follow-up period of 13.7 months (IQR: 8.3–20.6) in the training cohort and 10.5 months (IQR: 7.4–17.2) in the validation cohort, 19.0% (30/161) and 23.0% (18/79) of patients, respectively, achieved an objective response by RECIST v1.1 ($p = 0.559$). The radiomic feature model demonstrated a promising predictive performance, achieving an AUC of 0.913 (95% CI: 0.874–0.953) in the training cohort and 0.825 (95% CI: 0.700–0.949) in the validation cohort. Fat surpassing liver mass was the only MRI feature associated with an objective response ($p = 0.020$). When the MRI feature was combined with radiomic features, the predictive model further improved, yielding an AUC of 0.951 (95% CI: 0.924–0.979) in the training cohort and 0.835 (95% CI: 0.725–0.945) in the validation cohort. A significant correlation was observed between radiomic features and MRI features of intrahepatic lesions with a univariate analysis $p < 0.2$. **Conclusions:** Radiomic features derived from pretreatment MRI scans can effectively predict personalized objective responses to combination therapy with atezolizumab and bevacizumab in patients with unresectable or advanced HCC. Research Sponsor: National Natural Science Foundation of China; 82372037.

4105 Poster Session

Efficacy and safety of atezolizumab and bevacizumab with or without transarterial chemoembolization as first-line therapy for advanced hepatocellular carcinoma: An international multicenter real-world study.

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Background: Transarterial chemoembolization (TACE) combined with immunotherapy and targeted therapy provides a promising therapy for advanced hepatocellular carcinoma (HCC).This study aimed to compare the efficacy and safety of atezolizumab and bevacizumab combined with (TACE-Ate-Bev) or without TACE (Ate-Bev) as first-line treatment for advanced HCC. **Methods:** This international multicenter, retrospective study included 311 advanced HCC cases administered TACE-Ate-Bev (n = 152) or Ate-Bev (n = 159). Inverse probability of treatment weighting (IPTW) was employed to minimize bias. Overall survival (OS), progression-free survival (PFS), and adverse events (AEs) were observed. **Results:** The TACE-Ate-Bev group demonstrated significantly improved OS (26.8 [95% CI 23.1-NA] vs. 14.9 months [95% CI 11.4-19.9]; hazard ratio [HR] = 2.66 [95% CI 1.87-3.77], $p < 0.0001$) and PFS (16.0 months [95% CI 12.8-17.8] vs. 6.5 months [95% CI 5.4-7.6]; HR = 2.50 [95% CI 1.90–3.28], $p < 0.0001$) compared to the Ate-Bev group, especially across BCLC stage B (mOS: NA [95% CI 23.5-NA] vs. 15.6 months [95% CI 11.4-NA], $p < 0.0001$; mPFS: 16.9 months [95% CI 16.2-NA] vs. 6.7 months [95% CI 5.7-10.9], $p < 0.0001$) and BCLC stage C (mOS: 25.2 months [95% CI 19.7-NA] vs. 14.3 months [95% CI 10.1-20.5], $p = 0.00018$; mPFS: 12.8 months [95% CI 11.3-17.0] vs. 6.5 months [95% CI 5.0-7.7], $p < 0.0001$) disease. The superior efficacy of TACE-Ate-Bev indicated same trends after IPTW adjustment. Grade 3 or 4 AEs were observed in 36 patients (24.3%) in the TACE-Ate-Bev group and 34 (21.4%) in the Ate-Bev group. There was no statistically significant difference in the proportion of gastrointestinal bleeding between the TACE-Ate-Bev and Ate-Bev groups (9.9% vs. 10.1%, $p = 0.954$). Notably, patients with portal hypertension, portal vein tumor thrombus vp3-4, extrahepatic metastasis or Child-Pugh grade B exhibited improved OS and PFS in the TACE-Ate-Bev group versus the Ate-Bev group. **Conclusions:** TACE-Ate-Bev significantly improves OS and PFS with acceptable toxicity compared to Ate-Bev as first-line therapy for advanced HCC. Research Sponsor: None.

Factors associated with immunotherapy response for hepatocellular carcinoma.

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Background: Immunotherapy has shown remarkable progress in treating hepatocellular carcinoma (HCC) in recent years. We aim to investigate the clinical factors associated with treatment response to HCC immunotherapy in Asian population. **Methods:** We identifiedHCC patients receiving immunotherapy (nivolumab, pembrolizumab, atezolizumab, durvalumab, tremelimumab, ipilimumab; including monotherapies or combinations) from January 2008 to June 2024 from a population-based cohort in Hong Kong. Primary outcomes were all-cause mortality and hospitalization stratified by etiology of HCC [Viral-HCC, defined as hepatitis B virus (HBV)-related or/and hepatitis C virus (HCV)-related HCC vs non-viral-HCC], other clinical factors including age, sex, type 2 diabetes (T2D), cirrhosis, antiviral therapy for HBV, and history of receiving other oncological treatment (curative: surgical resection, liver transplant, radiofrequency ablation, microwave ablation; non-curative: transcatheter arterial chemoembolization and radiotherapy). Hazard ratios (HR) were estimated by Cox regression models. **Results:** This study included 1363 patients on immunotherapy (mean age 63.1 years, 84.2% male; 87.2% viral-HCC; 23.0% had prior curative therapy; 34.5% had prior non-curative therapy). Over 240-days of median follow-up, viral-HCC had similar risk of all-cause mortality (54.5% vs 58.9%, p = 0.169) and hospitalization (34.8% vs 30.9%, p = 0.360) compared to non-viral-HCC. Patients with prior curative therapy compared to those without had lower risk of all-cause mortality (HR 0.81 [95% CI: 0.69-0.95], p = 0.011). Among HBV-related HCC, those with antiviral treatment ≥2 years prior to immunotherapy were associated with lower risk of liver-specific mortality (HR 0.83 [95% CI 0.70-0.99], p = 0.036) and HCC-specific mortality (HR 0.80 [95% CI 0.67-0.96], p = 0.014). Patients with cirrhosis had higher risk of all-cause mortality (HR 1.42 [95% CI 1.18-1.71], p < 0.001). No associations with treatment response were observed in subgroups stratified by age < 60/ ≥60, sex, and T2D. **Conclusions:** Among patients with HCC receiving immunotherapy, treatment outcomes were similar in viral-etiologies and non-viral etiologies. Antiviral treatment improves treatment response in HBV-related HCC, while cirrhosis is detrimental to mortality outcomes. HCC immunotherapy following curative treatment, in contrast to non-curative therapies, has improved treatment response. Research Sponsor: None.

	All-cause mortality			Hospitalization		
	HR	95% CI	P value	HR	95% CI	P value
Viral-HCC	0.86	(0.70, 1.06)	0.169	1.14	(0.86, 1.51)	0.360
Age (<60/ ≥60)	0.91	(0.79, 1.06)	0.238	0.90	(0.76, 1.08)	0.276
Sex	0.98	(0.81, 1.18)	0.812	0.99	(0.78, 1.26)	0.939
T2D	1.00	(0.86, 1.15)	0.957	0.84	(0.70, 1.02)	0.082
Cirrhosis	1.42	(1.18, 1.71)	<0.001	1.23	(0.99, 1.52)	0.062
Curative therapy	0.81	(0.69, 0.95)	0.011	1.09	(0.88, 1.33)	0.434
Non-curative therapy	1.11	(0.96, 1.29)	0.147	1.60	(1.34, 1.92)	<0.001

Evolutionary divergence of the HLA-B genotype as a predictor of immune checkpoint inhibitor (ICI) therapy efficacy in hepatobiliary cancers.

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Background: The role of human leukocyte antigen class I (HLA-I) molecules in shaping the immune response to immune checkpoint inhibitors (ICIs) has been recognized in several solid malignancies. However, the prognostic significance of HLA-I characteristics in hepatobiliary cancers remains poorly understood. **Methods:** Patients with advanced hepatocellular carcinoma (aHCC) and biliary tract cancer (aBTC) receiving ICI-based therapy were prospectively enrolled (NCT03892577). Retrospective analyses were performed to evaluate the association between HLA-I evolutionary divergence (HED), HLA-I genotype, and HLA-I heterozygosity with clinical outcomes. HLA-I genotyping was conducted using germline DNA from peripheral blood, and HED was quantified based on the Grantham distance metric, which measures evolutionary divergence between HLA-I alleles. Patients were stratified into high and low HED groups using the 25th percentile as the cutoff. **Results:** A total of 118 patients (41 with aHCC and 77 with aBTC) were included in the analysis. High HED at the HLA-B genotype was significantly associated with improved overall survival (OS) in patients treated with ICIs ($p < 0.05$). Specifically, in aHCC patients, the median OS was 17.43 (95% confidence interval, 17.43-NE) months in the HLA-B HED^{high} group compared to 7.83 months (95% confidence interval, 4.13-NE) in the HLA-B HED^{low} group ($p < 0.05$). Similarly, in aBTC patients, the median OS was 12.7 (95% confidence interval, 9.07-20.90) months versus 9.8 (95% confidence interval, 6.40-13.5) months, respectively ($p < 0.05$). In contrast, HED at the HLA-B genotype did not exhibit a significant association with progression-free survival. **Conclusions:** This study demonstrates that the evolutionary divergence of the HLA-B genotype may serve as a prognostic biomarker for ICI therapy in hepatobiliary cancers. High HED at HLA-B is associated with improved OS, underscoring the potential role of HLA-I genetic diversity in modulating therapeutic response to ICIs. These findings provide a foundation for further investigations into HLA-mediated mechanisms underlying ICI efficacy in hepatobiliary cancers. More patients will be enrolled to validate the conclusions. Clinical trial information: NCT03892577. Research Sponsor: Beijing Natural Science Foundation; National High Level Hospital Clinical Research Funding; National Ten-thousand Talent Program.

Hepatic arterial infusion chemotherapy plus lenvatinib and PD-1 inhibitors as first-line treatment for hepatocellular carcinoma with high tumor burden and portal vein tumor thrombus.

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Background: Advanced-stage hepatocellular carcinoma (HCC) is usually associated with poor survival outcomes. Rapid tumor control usually benefits long-term outcomes, which could be hardly achieved by solely systematic targeted and immunotherapy in current guidelines. This study aimed to evaluate the efficacy of hepatic arterial infusion chemotherapy (HAIC) combined with lenvatinib and PD-1 inhibitors (HLP) as first-line treatment for HCC patients with high tumor burden and portal vein tumor thrombus (PVTT). **Methods:** This retrospective multi-center study screened advanced HCC patients who received HLP combination therapy as first-line treatment at ten centers from Jan 2021 to Dec 2023. The inclusion criteria included high tumor burden (up to seven criteria out), PVTT, no extra-hepatic metastasis, and liver function of Child-Pugh B7 or better. PD-1 inhibitors permitted 3 different products, including Tislelizumab. Tumor response was assessed using both RECIST 1.1 and mRECIST criteria. Survival outcomes were analyzed using Kaplan-Meier methods. The primary endpoint was overall survival (OS), while secondary endpoints comprised progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), as well as depth of response (DpR) within 3 months. Baseline time point was defined as start of any designed treatment except DpR related survival as 3 months after initial treatment. **Results:** A total of 94 patients were included. The median age was 53 years (range: 31-78) and 87.2% (82/94) were male. In all the patients, 58.5% (55/94) had a largest tumor diameter ≥10 cm, and 80.4% (74/92) had PVTT classified as Vp3 or Vp4. The median follow-up time was 13.3 (8.9-25.2) months, the 12-month OS rate was 75.6% (95% CI: 67.0-85.3), and the 24-month OS rate was 57.6% (95% CI: 46.9-70.7). Median PFS was 9.7 months (95% CI: 8.1-16.0), with 12- and 24-month PFS rates of 46.3% (95% CI: 37.1-57.8) and 32.1% (95% CI: 23.3-44.3), respectively. Based on RECIST 1.1 or mRECIST, the ORR was 42.6% (95% CI: 32.4-53.2) or 70.2% (95% CI: 59.9-70.2), and the DCR was 96.8% (91.0-99.3) or 100% (96.2-100), respectively. Regarding DpR within 3 months, 46.8% (44/94) of the patients had > 25% tumor diameter reduction per RECIST 1.1, while 73.4% (69/94) showed > 25% reduction per mRECIST. In subgroup analyses, DpR was significantly correlated with PFS and OS (see table), while largest tumor diameter, tumor number, and Vp classification had no correlation with survival outcomes. **Conclusions:** Combination of HLP as a first-line treatment for advanced HCC with high tumor burden and PVTT is promising, with high ORR and survival outcomes. DpR might be a predictor for survival. Clinical trial information: NCT06631326. Research Sponsor: None.

Outcomes		DpR≤25%		DpR>25%
PFS	Events/N	37/50		24/44
	Median (m)	6.8 (5.4-10.9)		16.0 (11.0-NR)
	P		0.004	
OS	Events/N	24/50		12/44
	Median (m)	19.2 (12.6-NR)		35.0 (24.5-NR)
	P		0.034	

4109 Poster Session

Molecular characteristics, treatment patterns, and survival outcomes in biliary tract cancers: A retrospective analysis from a high-prevalence region.

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Background: Biliary tract cancers (BTC) present significant challenges in management due to their aggressive nature and often late-stage presentation. We present demographic trends, molecular characteristics, treatment patterns, and survival outcomes. **Methods:** This retrospective study included patients diagnosed with BTC between March 2018 and September 2024. Survival analysis was done using the Kaplan-Meier analysis. **Results:** Total of 743 patients were diagnosed with BTC, median age of the cohort was 61 years (IQR 52-69); with F: M ratio being 1.15:1. Distribution according to the stage at presentation was: stage I (n=15, 2%), stage II (n=49,6.6%), Stage III (n=160, 21.5%) and stage IV (n=509, 68.5%). History of gallstones was reported in 183 patients (24.6%). Out of the total cohort, 436 patients (58.7%) had gallbladder cancers (GBCs) while 307 patients (41.3%) had cholangiocarcinoma (CCA), where n=202 (65.8%) were intrahepatic, n=22 (7.2%) were perihilar and n=33 (10.7%) were distal bile duct. Predominant histologic patterns among GBCs were: adenocarcinomas n=331 (75.9%), small cell carcinomas n=13(3%) adenosquamous n=11(2.5%), and others n=81(18.5%). Molecular testing was done in 132 patients (17.8%), out of which 11/132 (8.3%) had HER2 alteration, wherein overexpression was seen in n=3,while amplification was seen in n=8; TP53 mutation was seen in 21/132 (16%), while others alterations were MSI-high (n=2), TMB-high (≥10 mut/Mb) (n=3), PDL1 positive (n=24), FGFR(n=3), IDH (n=2), BRCA2 (n=2). Treatment and survival outcomes were available for 492 patients, surgery was done in 177 patients (35.9%), systemic therapy (adjuvant/palliative) was done in 431 (87.6%) patients while targeted or immunotherapy was used in 99 patients (20.1%). Median Overall survival (mOS) of the cohort was 16.1 months (13.6-18.6) with a median follow-up duration of 28.2 months (23.2 – 33.2). mOS for GBC was 10.8(8.2-13.3) months and CCA was11.6(9.3-14.0) months. mOS for Metastatic BTC was 9.6 months while for Non-metastatic it was 20.4 months($p<0.001$). The median mOS for patients with HER2 mutations, TP53 mutations, and PD-L1 positivity were 23.8 months, 16.6 months, and 10.0 months, respectively ($p = 0.165$). **Conclusions:** In high-prevalence countries like India, biliary tract cancer (BTC) management is challenged by advanced stage presentation, limited molecular testing and resource constraints. Efforts to enhance molecular testing and treatment access are critical for practicing precision oncology and improving treatment outcomes. Research Sponsor: None.

Comparison of outcomes between open and minimally invasive hepatic resections for hepatocellular carcinoma: A retrospective analysis.

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Background: Recent data from the United States indicate that the incidence of hepatocellular carcinoma (HCC) has tripled over the past 40 years, with risk factors like obesity-related fatty liver disease and chronic hepatitis C on the rise. Despite advances in treatment, the five-year survival rate remains low at 14%. Minimally Invasive Surgery (MIS) has garnered popularity in hepato-pancreato-biliary (HPB) procedures, comprising 1 in 13 cases. MIS offers advantages such as shorter hospital stays and reduced morbidity, with better outcomes. However, the safety and efficacy of MIS, specifically for HCC resection, remain underexplored. To address this gap, we conducted this study to evaluate and compare the outcomes of MIS vs. open surgical approaches for HCC resection. **Methods:** The 2016–2022 National Inpatient Sample (NIS) was utilized for this study. Patients with a primary procedural code for hepatic resection, categorized as either open or minimally invasive approaches, were identified. This cohort was further narrowed to include only patients diagnosed with hepatocellular carcinoma (HCC). Differences in common postoperative complications between open and minimally invasive approaches were analyzed. **Results:** We studied 3,595 hepatic resections for HCC, with 87.5% performed as open procedures and 12.5% as minimally invasive surgeries. Both approaches were predominantly conducted in males (70.9% vs. 75.6%, $p = 0.041$), with open resection patients being younger (mean age 63.94 vs. 66.67, $p < 0.01$). Open resections were associated with higher complication rates, including critical care needs (aOR 6.428, 95% CI 2.606–15.858, $p < 0.001$), sepsis (aOR 3.728, 95% CI 1.508–9.215, $p = 0.004$), acute kidney injury(AKI) (aOR 2.406, 95% CI 1.714–3.337, $p < 0.001$), bleeding (aOR 2.314, 95% CI 1.838–2.914, $p < 0.001$), and blood transfusion requirements (aOR 4.514, 95% CI 2.661–7.658, $p < 0.001$). Open procedures also resulted in higher mean hospital charges ($180,561 vs. $131,566, $p < 0.01$) and more extended hospital stays (8.5 vs. 5.3 days, $p < 0.01$). Despite these differences, mortality rates between open and minimally invasive approaches were similar (aOR 1.486, 95% CI 0.85–2.595, $p = 0.164$). **Conclusions:** Our study found that open hepatic resection for HCC is associated with a higher rate of complications, including bleeding, AKI , increased critical care needs, and blood transfusion requirements, compared to minimally invasive surgery. However, mortality rates between the two approaches remain comparable. With the rising incidence of HCC, transitioning toward MIS may provide notable benefits in reducing postoperative morbidity. Since most hepatic resections are still performed using open techniques, further research is necessary to enhance surgical outcomes and explore alternative strategies. Research Sponsor: None.

Association of gut microbiota with therapy efficacy and prognosis in biliary tract cancer.

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Background: Biliary tract cancers (BTC) are rising in incidence and have poor prognosis. Microbial exposure via gut–liver axis may contribute to their development and progression. We profiled the gut microbiome of patients with BTC and assessed its correlation with chemoimmunotherapy outcome. **Methods:** For this prospective study, we collected baseline stool samples from newly diagnosed patients with BTC treated at a single center. Microbiome profiles were generated using 16S rRNA gene sequencing. Microbial alpha (intrasample variability) and beta (interindividual variability) diversity indices were calculated and correlated with treatment outcome. Taxonomical differential abundance was quantified using MaAsLin2. Statistical analyses included descriptive statistics for demographics, Kaplan-Meier for survival & Spearman's correlation for microbiome-clinical outcome. **Results:** From May 2021 to October 2024, 72 patients were enrolled. Median age was 66 years (range: 29–86) with 43% females. Primary sites included intrahepatic cholangiocarcinoma (CCA) (61%), distal extrahepatic CCA (18%), hilar CCA (11%), gallbladder Ca (3%), and mixed (7%). Stages were I (14%), II (33%), III (46%), IV (7%). 52% underwent surgery (14% upfront/others post neoadjuvant), 74% progressed to stage 4 disease and 67% received immune check point inhibitors. Therapy responses included complete (CR 3%), partial (PR 19%), stable (SD 32%), and progressive (PD 28%). At a median follow-up of 20 mos, mPFS was 14.6 (8.3-NR) mos for entire cohort [8 (5–11) mos for stage 4 patients] and mOS was not reached. Microbiome analysis of stool samples provided by immunotherapy-treated patients (n = 26) suggested that disease control (DCR: CR/PR/SD) correlated with higher alpha diversity ($p = 0.063$), while progression showed a trend toward lower diversity across all indices. Beta diversity (calculated by Bray-Curtis distances) showed no significant differences by response or progression. Differential abundance analysis using MaAsLin2 identified significant microbial associations (LogFC > 1.5, adjusted $p < 0.25$) with treatment outcomes. DCR associated bacterial genera included *Ruminococcus*, *Subdoligranulum*, *Romboutsia & Collinsella*, while PD correlated with higher abundances of *Streptococcus*, *Eggerthella*, *Paraprevotella & Enterococcus*. Genera such as *Ruminococcus*, *Romboutsia*, *Coprococcus & Christensenellaceae R-7 group* were linked to non-progression, whereas *Parasutterella*, *Streptococcus*, *Prevotella-9 & Monoglobus* were elevated in progressive disease. **Conclusions:** Our preliminary results suggest that gut microbiome should be studied as a multidimensional biomarker for predicting therapy response/prognosis in BTC. Higher microbial alpha diversity may link with better immunotherapy responses, and specific microbial taxa may correlate with treatment outcomes. Research Sponsor: None.

CTC landscape during HCC immunotherapy.

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Background: The treatment of hepatocellular carcinoma (HCC), the third leading cause of global cancer death, has significantly improved with the advent of immune checkpoint inhibitor regimens. Circulating tumor cells (CTCs) contain the precursors of metastasis and can be serially sampled while patients receive therapy. Quantification of CTC dynamics during HCC treatment with immune checkpoint inhibitor therapy may yield early insight into the systemic anticancer response profile. **Methods:** We used a commercially available microfluidic CTC purification methodology followed by quantification of CTCs expressing HCC cell surface markers (EPCAM, ASGR1, GPC3) and PD-L1 from patients receiving immune therapies, prior to cycle 1 and cycle 3 of therapy. We also captured and correlated clinical data, including conventional markers of liver function (Child-Pugh score) and radiographic tumor response for correlation with early changes in CTC number. **Results:** In this pilot study,we collected a total of 29 specimens from 14 participants, 10 of whom provided serial samples. The quantities of CTCs detected was (median:10, range: 1-516); (median:1, range: 0-139) were PD-L1 high,(median: 8, range: 1-312) were PD-L1 medium, and (median: 3, range: 0-190) were PD-L1 low. There was no clear statistical difference in serial CTC enumeration data while on treatment, although the numbers of CTCs and CTC subsets numerically declined in many participants. **Conclusions:** There was no statistically significant relationship between CTC quantity and subsequent radiographic response. Future studies will involve enrollment of expanded numbers of participants, comparisons with circulating tumor DNA dynamics, and transcriptional profiling of CTCs to further explore these phenomena. Research Sponsor: UCCCC.

Deep learning-based contouring of Couinaud segments on CT: Utility for volumetric analysis of future liver remnant.

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Background: Hepatocellular carcinoma (HCC) is the most common primary liver tumor, and the liver is a frequent site of metastasis of other cancers. High tumor burden, proximity to hepatic vessels, and other comorbidities render only 30% of patients as candidates for curative treatment: transplantation, resection, or ablation. Surgical resection requires a 20 - 40% future liver remanent (FLR) to avoid post-operative complications. Delineation of the Couinaud segments is essential for volumetric analysis of FLR and targeted localization of tumors during pre-surgical treatment planning. Currently, manual annotation of the Couinaud segments in one CT volume can take two or more hours, which makes it cumbersome, and can benefit from automation. The purpose of this work is to develop an automated Couinaud segmentation tool for fast and accurate FLR estimation. **Methods:** Three CT datasets were used: 1) 161 patients from the public Medical Segmentation Decathlon (MSD) Hepatic Vessels dataset, 2) 43 patients with cirrhosis and metabolic diseases having ascites and splenomegaly imaged at the National Institutes of Health (NIH), and 3) 197 patients in the public TCIA Colorectal Liver Metastasis (CRLM) dataset. FLR annotation in the CRLM dataset was done by an expert radiologist. The Couinaud segments in the MSD and NIH datasets were manually annotated by two physicians using ITK-SNAP. The MSD and NIH datasets were used for training, while the CRLM dataset was reserved for testing. A 3D nnU-Net model was trained with default hyperparameters to outline the Couinaud segments. On the test dataset, the predicted Couinaud segments were overlaid on the FLR annotation, and metrics, such as Dice Similarity Coefficient (DSC), Hausdorff Distance (HD) error (in mm), and volume error (in cc) were calculated. The performance was compared to a previously described 3D U-Net model developed to quantify liver segmental volume ratio (LSVR) in patients with cirrhosis. **Results:** The 3D nnU-Net obtained a DSC of 0.99 $\pm$ 0.01 (IQR: 0.991, 0.998), HD error of 0.87 $\pm$ 1.83 mm (IQR: 0, 1.02), and volume error of 13.7 $\pm$ 28.1 cc (IQR: 3.4, 15.3). In contrast, the LSVR U-Net model attained a DSC of 0.97 $\pm$ 0.01 (IQR: 0.972, 0.984), HD error of 9.56 $\pm$ 3.61 mm (IQR: 7.14, 11.93), and volume error of 47.9 $\pm$ 51.8 cc (IQR: 24.5, 55.4). The 3D nnU-Net model achieved significantly different results for DSC ($p < 0.001$, large effect size 0.86), HD error ($p < 0.001$, large effect size 0.87), and volume error ($p < 0.001$, large effect size 0.91). **Conclusions:** The model showed acceptable generalizability to the external TCIA CRLM dataset. Future work may be directed towards accurate volumetric analysis on patients undergoing portal vein embolization to increase the FLR, and automatic tumor localization on specific Couinaud segments. Research Sponsor: None.

AI-driven prediction of post-transplant survival and stratification of HCC recurrence risk.

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Background: Traditional selection criteria (e.g., Milan, UCSF) and scoring systems (MELD/PELD) for liver transplant eligibility in hepatocellular carcinoma (HCC) often fail to capture the complex interplay of tumor biology, patient factors, and bridging therapies. Although Milan and UCSF yield similar 1-, 3-, and 5-year survival rates, the debate over expanded criteria highlights the need for refined, individualized risk-stratification tools. **Methods:** We retrospectively analyzed 21,182 HCC patients from the UNOS database to develop deep learning and Cox regression models for overall survival (OS). Models incorporated demographic (e.g., age, race), clinical (e.g., diabetes, MELD differences), and tumor-specific variables (e.g., tumor count, size tiers). Performance was compared to standard MELD-based calculations using 5-fold cross-validation, with primary endpoints of 1-, 3-, and 5-year survival. For recurrence risk, we used 15,801 records to train gradient boosting (XGBoost) and Cox models. Key variables included tumor characteristics (size levels, vascular invasion), recipient factors (insurance type, functional status, initial MELD/PELD), and alpha-fetoprotein (when available). Model performance was evaluated via area under the curve (AUC) and concordance index (c-index); external validation was performed for the recurrence model. **Results:** Cox Regression (time-to-event): Final multivariable models achieved c-indices of 0.611 for OS and 0.601 for progression-free survival (PFS). Stepwise Logistic Regression (mortality): Mean AUCs were 0.664 (1-year), 0.705 (3-year), and 0.758 (5-year). Random Forest Classifier: Slightly higher AUCs than logistic regression (0.663 at 1-year, 0.714 at 3-year, 0.762 at 5-year). Gradient Boosting (recurrence): 1-year recurrence predictions achieved AUC > 0.80, with microvascular invasion emerging as a key risk factor ($p<0.001$). Across approaches, incorporating multiple clinical and tumor-specific factors outperformed MELD-based models, consistently showing improved predictive accuracy. **Conclusions:** Machine learning–based models, including deep learning, random forests, and gradient boosting, offer enhanced risk prediction for post-transplant survival and HCC recurrence beyond traditional scoring criteria. These advanced tools enable more nuanced transplant selection, surveillance, and early intervention strategies, potentially improving long-term outcomes for HCC patients undergoing liver transplantation. Research Sponsor: None.

A phase II study of pevonedistat in combination with carboplatin and paclitaxel in advanced intrahepatic cholangiocarcinoma: ECOG-ACRIN EA2187.

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Background: Cholangiocarcinoma is a rare and aggressive malignancy with limited therapeutic options, particularly in advanced stages. Resistance to first-line chemotherapy underscores the urgent need for novel therapeutic strategies. Pevonedistat, a first-in-class NEDD8-activating enzyme inhibitor, demonstrated promising activity in this disease in a phase I trial. This study evaluates pevonedistat alone and in combination with carboplatin and paclitaxel in patients with advanced intrahepatic cholangiocarcinoma (ICC). **Methods:** This was a randomized, non-comparative Phase II trial investigating two treatment arms: pevonedistat monotherapy (Arm A) and pevonedistat combined with carboplatin and paclitaxel (Arm B). Both arms utilized a two-stage minimax design, targeting an objective response rate (ORR) of 30% (null hypothesis: 10%). Eligible patients had unresectable or metastatic ICC with progression after gemcitabine-based therapy. The primary endpoint was ORR per RECIST v1.1. Secondary endpoints included clinical benefit rate (CBR), progression-free survival (PFS), overall survival (OS), and safety. Toxicities were graded using CTCAE v5.0. **Results:** A total of 40 patients were enrolled, with 34 eligible and treated (17 per arm). Median follow-up was 29.3 months. No objective responses were observed in either arm. Stable disease was the best response in 35.3% (n = 12) of patients (11.8% Arm A, 58.8% Arm B). One patient on Arm B achieved stable disease lasting ≥24 weeks, corresponding to a CBR of 5.9% (95% CI: 0.1%-28.7%). Median PFS was 1.54 months (Arm A) and 2.92 months (Arm B). Median OS was 4.80 months (Arm A) and 6.54 months (Arm B). Grade 3 or higher toxicities occurred in 44.1% of patients, with higher incidence in Arm B (70.6% vs. 17.6% in Arm A). Most common toxicities included fatigue, cytopenias, febrile neutropenia, nausea/vomiting, among others. Two treatment-related fatalities were reported on Arm B: sepsis and colonic perforation. **Conclusions:** Pevonedistat, alone or in combination with carboplatin and paclitaxel, did not demonstrate sufficient efficacy to warrant further evaluation in advanced ICC. These findings highlight the challenges in treating this aggressive malignancy. Despite the rarity of ICC, the rapid accrual of this study during a global pandemic indicates the potential for continued exploration of novel therapeutic approaches in this disease. Clinical trial information: NCT04175912. Research Sponsor: NCI/NCTN.

Whole-genome sequencing of biliary tract cancer: Uncovering the genomic origins of evolutionary trajectories.

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Background: Biliary tract cancers (BTC) are rare, highly aggressive malignancies with limited treatment options, leading to consistently poor outcomes. An improved understanding of BTC tumor evolution could inform enhanced screening strategies, identify useful prognostic markers, and discover novel therapeutic targets. **Methods:** We performed whole genome and transcriptome sequencing (WGTS) at high depth ($>$ 80X) on a prospective cohort of BTC tumors. After detecting mutations and mutational signatures, we developed two novel methods for driver identification and evolutionary reconstruction. First, we created new oncogene and tumor suppressor-specific models that integrate copy number profiles, structural variant breakends, and expression changes to distinguish structural drivers from neutral chromosomal rearrangements. Second, we applied population genetics techniques to fit demographic models to tumor allele frequencies across 20 paired primary and metastatic samples. **Results:** We analyzed 130 tumor samples from 110 patients, representing the largest BTC whole-genome cohort to date. We identified hypermutated tumors (50-150 mutations/mb) with distinct etiologies, including mismatch repair deficiency, platinum exposure, tobacco use, and aristolochic acid-related damage, the latter of which was associated with response to immunotherapy. Ourintegrated-driver approach identified an association between selection on *RAD23A* and an increased structural variant load, resulting in a tandem-duplicator-like mutational phenotype. This also revealed an underappreciated impact of *SMAD4* in BTC, which is inactivated through multiple mutation types in 12%. Notably, *BAP1* mutations occurred in 24% of cases, including 4% that were inactivated through deletion of the *BAP1* promoter that lowered transcript expression, a previously undescribed mechanism. By pairing clinical data to the genomics, we observed a co-occurrence of *BAP1* mutations and *FGFR2* fusions in small-duct, mass-forming intrahepatic cholangiocarcinomas. These mutations were mutually exclusive with *TP53* mutations, which were enriched in patients with primary sclerosing cholangitis. Finally, our novel method for subclonal population reconstruction on paired samples illuminated recent tumor evolutionary dynamics and identified an *ARID1B* fusion with a potential role in metastasis. **Conclusions:** This study uncovered novel genomic mechanisms underlying the evolutionary origins of BTC beyond those previously identified with exome and panel sequencing, highlighting the value of WGTS. These results highlight the complex genomic heterogeneity of BTC, with potential implications for precision therapy. Research Sponsor: Ontario Institute for Cancer Research; Princess Margaret Cancer Foundation; Marathon of Hope.

Real-world validation of the risk estimation of tumor recurrence after transplant (RETREAT) score: Insights from UNOS data on hepatocellular carcinoma recurrence after liver transplant.

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Background: For over two decades, established criteria have guided the selection of liver transplantation (LT) candidates in hepatocellular carcinoma (HCC), yet recurrence remains a significant clinical challenge with limited treatment options. The Risk Estimation of Tumor Recurrence After Transplant (RETREAT) score was developed to address this gap. Further validation is needed to confirm its utility in real-world settings. **Methods:** We conducted a validation study using the United Network for Organ Sharing (UNOS) database to evaluate the predictive performance of the RETREAT score in adult liver transplant recipients with HCC from 2009 to 2024. The analysis included 4,975 patients. Kaplan–Meier survival analysis was performed, and recurrence rates were compared across RETREAT score groups using the log-rank test. The predictive accuracy of the RETREAT score for HCC recurrence was assessed by calculating the concordance index (C-index), area under the ROC curve (AUC) evaluating the model's ability to discriminate between recurrence and non-recurrence events. **Results:** Among the 4,975 liver transplant recipients with hepatocellular carcinoma (HCC), the distribution of the RETREAT score was as follows: 13 patients (0.26%) had a score of 0, 1,713 patients (34.43%) had a score of 1, 1,981 patients (39.81%) had a score of 2, 524 patients (10.53%) had a score of 3, 526 patients (10.57%) had a score of 4, and 218 patients (4.38%) had a score $\geq$5. Kaplan–Meier survival analysis demonstrated a significant association between the RETREAT score and HCC recurrence ($p < 2e\text{-}16$). The hazard ratio for recurrence with each unit increase in the RETREAT score was 1.685 (95% CI: 1.574 to 1.803). The model's predictive accuracy, as assessed by the C-index, was 0.697 (95% CI: 0.668–0.725), and the AUC was 0.684 (95% CI: 0.655–0.713). **Conclusions:** The RETREAT score demonstrates a C-index of 0.697 in predicting HCC recurrence after liver transplantation. This model offers valuable risk stratification but could benefit from further refinement to improve its predictive accuracy. Research Sponsor: None.

Conversion therapy for initially unresectable intrahepatic cholangiocarcinoma: A multicenter real-world study.

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Background: Currently, studies on conversion therapy for intrahepatic cholangiocarcinoma (ICC) are relatively limited. Effectiveness and optimization strategies of conversion therapy in real world remain unclear. This study aims to analyze the efficacy of locoregional combined with systematic therapy in patients with unresectable ICC, optimizing conversion therapy strategies by retrospectively. **Methods:** In this multicenter retrospective study, patients with unresectable ICC who received hepatic arterial infusion chemotherapy combined with ICIs and target therapy were reviewed. Overall survival (OS), progression-free survival (PFS) , objective response rate (ORR) , disease control rate(DCR)(assessed by mRECIST criteria) and safety were analyzed. **Results:** Between June 2018 to May 2024,a total of 341 patients from six centers were included in this study. The median follow-up time was 21.7 months.Among them, 313 patients with complete imaging evaluations are eligible for efficacy analysis. Of which, 20 patients achieved complete response (CR), 93 patients partial response (PR), 161 patients stable disease (SD), illustrating an ORR of 36.1% and a DCR of 87.5%. Among them, 65 patients successfully underwent conversion surgery, with a median duration of conversion therapy of 4.1 months. Radical resection was achieved in 39 patients within the surgical cohort, and 3 patients demonstrated pathological CR. Systemic therapy regimens with the highest conversion success rates included apatinib plus toripalimab (42.9%), lenvatinib plus tislelizumab (32.4%), and apatinib plus tislelizumab (30.8%). Patients with tumor diameters less than 10 cm and those with unilobar tumor were more likely to achieve successful conversion. After propensity score matching (PSM) to balance baseline characteristics (ratio = 1, caliper = 0.01), the surgical group exhibited better survival outcomes compared to the non-surgical group (not reached vs. 27.2 months, hazard ratio: 0.36, 95% CI: 0.61–0.81, p= 0.001). The median PFS was 13.0 months in the surgical group versus 8.0 months in the non-surgical group (hazard ratio, 0.57; 95% CI, 0.30 to 1.09; p= 0.088).Within the surgical cohort, the 2-year survival rates for patients with palliative surgery and radical resection were 51.3% and 26.9%, respectively (p= 0.051). All patients experienced treatment-related adverse events (TRAEs), but no treatment-related deaths occurred. The incidence of Grade 3-4 TRAEs was 28.6%. **Conclusions:** Locoregional combined with systemic therapy is an effective strategy for conversion treatment. Conversion surgery offers substantial survival benefits, while palliative surgery may also serve as a viable therapeutic option. Research Sponsor: None.

4119 Poster Session

Clinico-molecular characteristics and enhanced efficacy of immune checkpoint inhibitors in *TP53*-mutated advanced biliary tract cancer.

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Background: *TP53* mutations are frequent genetic alterations in cancers and also prevalent in biliary tract cancer (BTC). In non-small cell lung cancer, *TP53* mutations have been reported to enhance immune checkpoint inhibitor (ICI) efficacy and improve outcomes. However, their impact on BTC remains unclear. This study investigated the clinico-molecular characteristics, prognosis, and ICI efficacy in *TP53*-mutated BTC. **Methods:** Patient data were collected from the SCRUM-Japan GOZILA and MONSTAR-SCREEN-1/2 databases (Japan) and the Duke university and Mayo clinic databases (U.S.), which included patients receiving first-line ICI therapy. Comparisons between *TP53* wild-type (WT) and mutation groups were performed in the Japanese cohort. Subsequently, analyses were expanded to include U.S. patients, focusing on comparisons between non-ICI and ICI groups. Tumor Immune Dysfunction and Exclusion (TIDE) scores were calculated using MONSTAR-SCREEN-2 whole transcriptome sequencing (WTS) data to evaluate ICI responsiveness, and gene set enrichment analysis (GSEA) explored pathways associated with *TP53* mutations. **Results:** In the Japanese cohort (n=594), *TP53* mutations were identified in 311 patients (52.4%). *KRAS*, *ERBB2*, *CDKN2A*, and *SMAD4* alterations were more frequent in the *TP53* mutation group, while *IDH1*, *BAP1*, and *FGFR2* fusions were more common in the WT group. Multivariable analysis showed *TP53* mutations were independent prognostic factors for poor outcomes (progression-free survival [PFS]: HR 1.37, 95% CI: 1.11–1.69, P=0.003; overall survival [OS]: HR 1.36, 95% CI: 1.06–1.75, P=0.017). Incorporating the U.S. cohort (n=625; non-ICI: 548; ICI: 77), no significant differences in overall response rate (ORR) or disease control rate (DCR) were observed in the non-ICI group between the groups. However, in the ICI group, *TP53* mutations tended to show higher ORR (21.1% vs. 38.5%, P=0.16) and DCR (47.4% vs. 66.7%, P=0.14). In the non-ICI group, *TP53* mutations were associated with worse PFS (HR 1.46, median PFS: 7.4 vs. 5.3 months, P<0.001), whereas, in the ICI group, no significant difference was observed; however, a trend toward better PFS was seen in the *TP53* mutation group (median PFS: 5.0 vs. 6.4 months, P=0.163). TIDE scores were significantly lower in the *TP53* mutation group, indicating higher ICI responsiveness. GSEA revealed enrichment of oxidative phosphorylation and hypoxia pathways. **Conclusions:** *TP53* mutations are independent prognostic factors for poor outcomes in BTC. However, patients with *TP53* mutations may derive greater benefits from ICIs, underscoring the importance of tailored therapeutic strategies in *TP53*-mutated BTC. Research Sponsor: None.

Genomic and outcome analysis of recurrent versus de novo metastatic pancreatic ductal adenocarcinoma (PDAC) receiving systemic therapy: Results from the Australian MoST and CaSP screening programs.

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Background: The genomic and prognostic characteristics of recurrent (R, from curative surgery) v *de novo* (D) presentation in metastatic PDAC patients (pt) requiring systemic therapy (rx) remain underexplored. We examined the difference in genomic alterations (alts), overall survival (OS), and outcome to matched rx according to disease presentation (DP). **Methods:** The PDAC cohorts from the Australian Molecular Screening and Therapeutics (MoST) and Cancer Screening Programs (CaSP) completed sequencing from 2016 to July 2024 were analysed; archival tissue was sequenced using genomic profiling platforms (mainly TSO500 and FoundationOne CDx). Frequencies of genomic alts were compared between R and D groups; significance was assessed using Chi-square tests with the Benjamini-Hochberg method ($q < 0.05$). OS was calculated from the start of initial rx using Kaplan-Meier method, with hazard ratios (HR) from Cox regression used for comparison. OS outcomes were stratified by matched versus unmatched rx in pts harbouring genomic alts within clinically actionable Tier 1-3 categories per TOPOGRAPH knowledge base criteria. **Results:** 949 pts with PDAC with valid genomic results across both programs were included. The *KRAS* alts were numerically more frequent in D (n = 434/491, 88%, p = 0.02) than R (n = 380/458, 82%) groups. Both *CDKN2A* and *SMAD4* alts were enriched in the D group (*CDKN2A*, D: 248, 51% v R: 157, 34%; *SMAD4*, D: 139, 29% v R: 85, 19%, $p < 0.001$ both). Among the 821 pts who started systemic rx, those with R PDAC (n = 411) showed longer median OS compared to those with D PDAC (n = 410, 18.9 v 13.0 months, mo; HR 0.59, 95% CI 0.49-0.69, $p < 0.001$). Genomic *CDKN2A* alts were associated with worse OS (median 13.4 v 16.5 mo, HR 1.34, 95% CI 1.14-1.58); most favourable prognosis was seen in 267 pts with *CDKN2A* wildtype in the R group (median 22.1 mo, 95% CI 17.4-25.9). After adjusting for both *CDKN2A* and *SMAD4* alts, R group remained associated with a lower risk of death than D group (HR 0.61, 95% CI: 0.51-0.72, $p < 0.001$). Pts who received active matched rx (n = 23) showed longer OS than those who received unmatched rx (n = 314) in both D (30.1 v unmatched 14.0 mo) and R groups (34.6 v 24.1 mo). The prevalence of specific *KRAS* mutations showed no significant differences between D and R groups, including G12D (D: 192, 39% v R: 167, 36%, p = 0.44), G12V (D: 126, 26% v R: 113, 25%, p = 0.78), G12R (D: 59, 12% v R: 50, 11%, p = 0.67), G12C (D: 6, 1% v R: 10, 2%, p = 0.37), and Q61 mutations (D: 37, 8% v R: 26, 6%, p = 0.31). There were no differences in alts in *TP53*, *ARID1A*, *BRCA1/2*, or other DNA repair pathway genes. **Conclusions:** Genomic and prognostic differences were seen in metastatic PDAC according to presentation, with *CDKN2A* alts enriched in *de novo* cases and associated with poor OS, emphasising the need to consider stratification of DP in trials and observational studies. Research Sponsor: None.

First results of an open-label, single arm phase II trial investigating the efficacy and safety of trifluridine/tipiracil combined with irinotecan as a second line therapy in patients with cholangiocarcinoma.

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Background: Cholangiocarcinoma (CCA) is a rare and aggressive malignancy with poor prognosis. Although firstline therapy with gemcitabine, cisplatin and durvalumab has been established based on the TOPAZ-1 trial, treatment options for subsequnt therapies remain limited. The TRITICC study investigated the combination of trifluridine/tipiracil (FTD/TPI) and irinotecan in patients with disease progression after firstline treatment. **Methods:** TRITICC was a phase IIA, interventional, prospective, open-label, non-randomized, exploratory, multicenter, single-arm trial. Adult patients with histologically confirmed, locally advanced or metastatic biliary tract cancer received FTD/TPI (25 mg/m² BSA, BID, orally, days 1–5 of each 14-day cycle) combined with irinotecan (180 mg/m² on day 1 of each cycle). Progression free survival (PFS) was the primary endpoint. Secondary endpoints included the PFS rate at 4 months, median overall survival (OS), objective response rate (ORR), and quality of life. The trial was registered with ClinicalTrials.gov (NCT04059562) and EudraCT (2018-002936-26). **Results:** 28 patients were enrolled across six sites in Germany. The median PFS was 3.1 months (95% CI: 2.0–7.5), with PFS rates of 35% (95% CI: 21%–58%) at 4 months, 30% (95% CI: 17%–54%) at 6 months, and 13% (95% CI: 4.7%–37%) at 12 months. PFS and PFS rates were higher in patients with intrahepatic CCA (iCCA). The OS rates were 74% (95% CI: 59%–93%) at 6 months and 38% (95% CI: 22%–68%) at 12 months. Similar to the PFS rates the OS rates were higher in iCCA. Among 27 evaluable patients, partial responses were observed in 3 patients (11.1%, 2 iCCA, 1 eCCA), stable disease in 11 patients (40.7%, 7 iCCA, 4 eCCA). Thirteen patients (48.1%, 7 iCCA, 6 eCCA) experienced disease progression. Outcomes due to tumor location will have to be examined in higher patient numbers. The most frequently reported adverse events included neutropenia, thrombocytopenia, gastrointestinal symptoms and fatigue. The mean Global Health Status score (EORTC QLQ-C30) declined moderately from 56.2 at screening to 46.4 at the end of treatment. No severe, unmanageable or unexpected toxicities were reported. **Conclusions:** The combination of FTD/TPI and irinotecan demonstrated promising efficacy and manageable safety in CCA patients progressing after first-line gemcitabine-based therapy, aligning with recent findings in comparable populations (e.g., Tella et al.). Further investigations are warranted to validate these results. The NIFTY trial suggested that pegylated irinotecan may enhance efficacy compared to conventional irinotecan, a hypothesis that will be explored in the planned follow-up TRITICC-2 study. The study was funded by Servier Deutschland GmbH and Servier Affaires Médicale. Clinical trial information: NCT04059562. Research Sponsor: None.

4122 Poster Session

Sequential or up-front triple combination with durvalumab, tremelimumab, and bevacizumab for patients with unresectable hepatocellular carcinoma (AIO-MONTBLANC): Safety interim analysis.

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Background: The combination of immune checkpoint inhibitors (ICI) durvalumab (durva) and tremelimumab (treme) has been approved for first-line (1L) therapy for advanced hepatocellular carcinoma (aHCC) and represents an alternative to combined atezolizumab and bevacizumab (bev). The MONTBLANC trial evaluates the efficacy and safety of combined durva, treme and bev in patients (pts) with aHCC (NCT05844046). **Methods:** This investigator-initiated, international, randomized phase 2 trial is the first to investigate the combination of durva, treme and bev. 70 pts with aHCC not amenable to curative treatment or locoregional therapy and preserved (Child-Pugh A) liver function are randomized in a 1:1 ratio to an early escalation arm (A) or triple treatment arm (B). Pts in arm A initially receive durva+treme with the addition of bev upon detection of disease progression or failure to achieving objective radiological response. Pts in arm B receive upfront durva, treme and bev. Durva, treme and bev are given in standard doses. The primary endpoint is overall response rate. Secondary endpoints include overall survival, progression-free survival and safety. We present the data of the second planned safety interim analysis. **Results:** 25 pts (arm A: 14, arm B: 11) were included in this analysis (04/2023 – 08/2024). Patients in arm A had a lower proportion of ECOG 0 (A: 78.6% vs B: 90.9%), higher proportion of Child Pugh A6 (A: 21.4% vs B: 9.1%), BCLC C (A: 78.6% vs B: 63.6%), macrovascular invasion (A: 42.9% vs B: 36.4%) and AFP ≥400 ng/mL (A: 42.9% vs B: 18.2%). Most adverse events (AE) were grade (G) 1 or 2. In arm A, there were 17 G3 AE, 1 G4 AE and 4 G5 AE. In arm B, 4 G3 AE and 1 G5 AE occurred. 18 serious AE (SAE) occurred in arm A and 2 SAE in arm B. There was one treatment-related death in arm A (ICI hepatitis) and none in arm B. In the first 6 months on treatment, there were no significant changes in ALBI score, Child Pugh score or ECOG performance status in both arms. **Conclusions:** This planned safety interim analysis did not reveal signals of unmanageable toxicity or deteriorating liver function through the addition of bev to durva/treme in the 1L treatment of pts with aHCC. Clinical trial information: NCT05844046. Research Sponsor: Astra Zeneca.

Comparative efficacy of cabozantinib or lenvatinib following atezolizumab plus bevacizumzb in patients with advanced hepatocellular cancer.

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Background: Atezolizumab plus bevacizumab is the most commonly utilized first-line therapy for advanced HCC. However, the optimal choice for second-line treatment remains uncertain, particularly between different tyrosine kinase inhibitors including lenvatinib and cabozantinib. This study aims to compare survival outcomes of patients with metastatic HCC who received either lenvatinib or cabozantinib as second-line therapy following frontline treatment with atezolizumab plus bevacizumab. **Methods:** This retrospective cohort study utilized the TriNetX database, a large-scale platform providing access to deidentified electronic medical records from over 130 million patients across 94 healthcare organizations in the United States. The study included patients diagnosed with metastatic HCC (ICD-10 codes: C22, C22.8) who were aged 18 years or older, diagnosed between January 2019 and October 2024, and had received first-line chemotherapy with atezolizumab and bevacizumab. The cohort was divided into two groups: one receiving lenvatinib and the other cabozantinib as second-line therapy. The primary outcome was overall survival (OS), compared between the two treatment groups using 1:1 propensity score matching (PSM) to balance baseline demographics and comorbidities. Kaplan-Meier survival analysis, log-rank tests, and hazard ratios (HR) were employed to assess differences in OS. **Results:** Between January 2019 and October 2024, a total of 552 patients met the study criteria, including 397 patients who received Lenvatinib and 155 patients who received cabozantinib as second-line therapy. Median age was similar in two groups (65.2 vs 65.9 yrs). There were no differences between the two groups with respect to gender, albumin or bilirubin levels. Lenvatinib group had lower proportions of white patients (44.1% vs 55.3%). After PSM (matched on age, race, gender, albumin and bilirubin), the final analysis included 151 patients in each treatment group. Kaplan-Meier survival curves demonstrated no statistically significant difference in OS between the two groups (median OS: 16.6 vs 10.9 months; HR: 0.809; 95%CI: 0.576-1.136; p=0.597). **Conclusions:** This retrospective cohort study found no significant difference in OS in pts with metastatic HCC treated with lenvatinib or cabozantinib as second-line therapy following atezolizumab plus bevacizumab. These findings suggest that both agents may offer comparable survival benefits, highlighting the need for further prospective studies to refine second-line treatment strategies for advanced HCC. Research Sponsor: None.

Molecular profile of hepatocellular carcinoma (HCC) in older (OA) versus younger adults (YA) receiving tyrosine kinase inhibitors: Does age matter?

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Background: While age is not an independent risk factor for poor outcomes it can have significant influence on outcomes in HCC. The median age of diagnosis is 65 years, and HCC is associated with significant geriatric comorbidities. Further, multi-kinase inhibitors (MKIs) are associated with up to 60% of grade 3-4 toxicities. We aim to analyze survival association with age in HCC and identify molecular markers, associated with survival in older patients with HCC receiving tyrosine kinase inhibitors (TKIs). **Methods:** 1473 HCC specimens with DNA/RNA sequencing were profiled at Caris Life Sciences. The study cohort was stratified based on median age into two groups: OA: age $>$ 65 and YA: age $<$ = 65. Real-world overall survival (OS) information was obtained from insurance claims data, and Kaplan–Meier estimates of OS were calculated from specimen collection to last clinical contact; and MKI time on treatment (TOT) from the initiation to termination of treatment. Hazard ratios (HR) and p-values were calculated using the Cox proportional hazards model and the log-rank test, respectively. **Results:** Median OS (mOS) among patients with OA was 14.8 months(m) vs 17.1m among YA (HR: 1.18, $p < 0.01$). The difference in mOS was even more pronounced among White OA (HR: 1.43, $p < 0.0001$) and Asian/Pacific Islanders (HR:1.62, p = 0.084). Interestingly, although not statistically significant, OA was associated with longer mOS in Black/African Americans (HR: 0.73, p = 0.082). OA was not associated with MKI-TOT such as sorafenib or cabozantinib. However, OA was associated with a shorter TOT (HR 1.6, $p < 0.01$) on lenvatinib (len). No molecular alterations were statistically significantly different between the two age groups on len. CTNNB1, TP53, CDKN2A mutations and PDL1+ were among the most differentially altered and were more common in OA. DNAJB1-PRKACA fusions were prevalent only in YA (13%, potentially representative of Fibrolamellar HCC), while SLC45A2-AMACR fusions were more prevalent among OA (6.6 vs 1.1%). Multivariate analysis revealed that OA was independently associated with shorter len-TOT (HR 1.6, p 0.01), while CTNNB1 mutations and DNAJB1-PRKACA fusions were independently associated with longer len-TOT (HR 0.4-0.5, both $p < 0.05$). **Conclusions:** OA was associated with differing survival trends between whites and Asian/PI compared to Black/AA. Further, OA was associated with shorter len-TOT, potentially due to anti-angiogenic toxicity. Our limitations include an inability to investigate race-based differences on len-TOT due to small sample sizes (Black/AA: n = 18, Asian/PI: n = 15) and the lack of toxicity and geriatric assessment data. Future studies including race, geriatric assessments and toxicity profiles should be considered to understand survival and tolerability differences. Research Sponsor: None.

Development and validation of a prognostic risk score for hepatocellular carcinoma recurrence post–liver transplant: Insights from the UNOS database.

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Background: For over two decades, the criteria for liver transplantation (LT) in hepatocellular carcinoma (HCC) have been well-established, yet recurrence remains a major clinical challenge. This recurrence contributes to inferior post-LT survival in HCC patients compared to those without HCC. Prognostic index could serve as a valuable tool to identify patients who may benefit from adjuvant therapies and guide standardized post-LT HCC surveillance, which currently varies across transplant centers. **Methods:** We developed and validated a predictive model using the United Network for Organ Sharing (UNOS) database, analyzing adult liver transplant recipients with hepatocellular carcinoma (HCC) from 2009 to 2024, including 4,970 patients. Univariable analysis identified variables associated with 1-year, 3-year, and 5-year post-transplant HCC recurrence, applying a strict p-value threshold (< 0.01). Significant variables were selected for multivariable logistic regression to build the model. Internal validation was performed for each time point using Receiver Operating Characteristic (ROC) curve analysis and confusion matrix evaluation, with the best-performing model selected based on these metrics. **Results:** The most significant model was derived using 3-year recurrence as the outcome. The final model included the pre-transplant Model for End-Stage Liver Disease (MELD) score ($p = 0.02$), worst tumor histology grade ($p < 0.001$), and total tumor diameter ($p = 0.03$). The final logistic regression equation is as follows: $\log(1-p/p) = -3.9630 - 0.0621 \times$ Initial MELD score + $0.7657 \times$ Worst tumor histology grade + $0.1084 \times$ Total tumor diameter. Internal validation results showed an AUC of 0.761 (95% CI: 0.718 - 0.804), accuracy of 0.769 (95% CI: 0.757 - 0.7807), sensitivity of 77.2%, and specificity of 65.0% for 1-year recurrence. For 3-year recurrence, the model demonstrated an AUC of 0.733 (95% CI: 0.702 - 0.763), accuracy of 0.6696 (95% CI: 0.6563 - 0.6827), sensitivity of 66.7%, and specificity of 70.9%. For 5-year recurrence, the AUC was 0.714 (95% CI: 0.685 - 0.743), with accuracy of 0.655 (95% CI: 0.641 - 0.668), sensitivity of 65.2%, and specificity of 68.6%. **Conclusions:** We have developed and validated a predictive model for HCC recurrence following LT using UNOS data. This model shows promising performance, particularly for predicting 1-year recurrence, and may potentially serve as a useful tool for guiding post-transplant management and surveillance strategies. Research Sponsor: None.

Transarterial chemoembolization plus donafenib and immune checkpoint inhibitors for intermediate hepatocellular carcinoma (CHANCE2410): A propensity score matching analysis.

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Background: Hepatocellular carcinoma (HCC) has high incidence and mortality, with over 80% of patients diagnosed at intermediate or advanced stages, limiting surgical options and worsening prognosis. Transarterial chemoembolization (TACE) is the standard treatment for intermediate HCC, inducing tumor ischemia and hypoxia, which alters the immune microenvironment and promotes immune activation. Combining TACE with immune checkpoint inhibitors (ICIs) and tyrosine kinase inhibitors (TKIs) has shown promise in enhancing treatment efficacy. Trials like EMERALD-1 and LEAP-012, along with real-world studies, suggest that TACE plus ICIs and TKIs improves progression-free survival (PFS) in intermediate HCC patients compared to TACE monotherapy. Donafenib, an oral TKI, has shown superior overall survival compared to sorafenib, being recommended as first-line treatment for advanced HCC in China. However, large real-world studies on the combination of TACE plus donafenib and ICIs in intermediate HCC are scarce. This study aims to compare the efficacy and safety between the combination therapy and the TACE monotherapy for intermediate HCC in a real-world setting. **Methods:** This nationwide, multicenter, retrospective cohort study included patients with intermediate HCC receiving either combination therapy or TACE monotherapy between January 2021 and May 2024 in China. The primary outcome was PFS. The secondary outcomes included overall survival (OS) rate, objective response rate (ORR) and safety. Tumor response was evaluated according to the mRECIST criteria. 1:1 propensity score matching (PSM) analysis was employed to minimize bias. Cox proportional-hazards regression model was used to analyze factors affecting PFS and OS. **Results:** A total of 364 patients were enrolled, with 192 receiving combination therapy and 172 receiving TACE monotherapy. After PSM, 127 patients from each group were included for analysis. The median PFS were significantly longer in the combination therapy group than it in the TACE monotherapy group (19.6 months [95% CI, 14.9-24.4] *vs.* 15.3 months [95% CI, 12.8-17.8], HR 0.647 [95% CI, 0.464–0.903], $p = 0.010$). The OS rate was higher in the combination therapy group (94.8% *vs.* 83.5%, 1-year OS rate; 76.4% *vs.* 64.8%, 2-year OS rate; HR 0.542 [95% CI, 0.327–0.989], $p = 0.016$). The ORR was also higher in the combination therapy group (78.9% *vs.* 62.5%, $p = 0.002$). Grade 3 or 4 adverse events from any cause were observed at a rate of 12.5% and 5.5% in the combination and monotherapy groups, respectively. Multivariate analysis identified combination therapy as an independent prognostic factor for both longer PFS and OS. **Conclusions:** Compared to TACE monotherapy, TACE plus donafenib and ICIs offers superior OS and PFS, which may be a viable first-line treatment option for intermediate HCC. Research Sponsor: None.

Hepatitis B virus reactivation in hepatocellular carcinoma patients undergoing immune checkpoint inhibitor and concurrent antiviral prophylaxis agents: A prospective observational study.

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Background: Immune checkpoint inhibitors (ICIs) have been recommended for the treatment of advanced hepatocellular carcinoma (HCC). However, due to the potential hazard of hepatitis B virus (HBV) reactivation, all ICI-related phase 3 studies had strict restrictions on HBV-DNA load (e.g., < 500IU/ml). Meanwhile, delayed immunotherapy may lead to poor prognosis for patients with high HBV-DNA load. This study aims to compare the HBV reactivation between HCC patients with low or high HBV-DNA load undergoing ICIs and concurrent antiviral prophylaxis agents. **Methods:** This prospective, observational study (NCT04680598) recruited HCC participants who were consecutive hepatitis B surface antigen (HBsAg)-positive and received concurrent antiviral prophylaxis agents and initial ICIs. Participants were divided into low group (HBV-DNA≤500 IU/ml) and high group (HBV-DNA > 500 IU/ml) according to the baseline HBV-DNA level. HCC patients without ICIs from NCT02973685 were also included for analysis. The primary endpoint was the incidence of HBV reactivation. The secondary endpoints included HBV reactivation-associated hepatitis, ICIs disruption, overall survival (OS) and progression-free survival (PFS). **Results:** Between December 25, 2020 and February 23, 2024, a total of 1015 participants were enrolled: 356 in the low group and 659 in the high group. The median age was 51 years (range, 18-84) with majority being males (89.2%) and hepatitis Be antigen (HBeAg) positive (18.1%). Most participants did not receive previous anticancer treatment (84.5%). Participants in the high group were present with significantly higher HBeAg rate (7.0% vs 24.1%, $p< 0.001$), higher ALBI grade 2-3 rate (33.7% vs 49.9%, $p< 0.001$), larger tumor size (9.3 vs 10.9 cm, $p< 0.001$), more advanced BCLC stage C (72.5% vs 83.3%, $p< 0.001$). A significantly higher proportion of participants in the low group had previously received antiviral prophylaxis agents (16.3% vs 3.6%, $p< 0.001$). The HBV reactivation rate was 4.5% in the low group and 6.1% in the high group (relative risk, 1.24; 95% confidence internal [CI], 0.81-1.89, $p= 0.30$). The frequencies of HBV reactivation-associated hepatitis were 1.7% and 2.3%, respectively ($p= 0.53$). There were 92 participants (25.8%) in the low group and 201 participants (30.5%) in the high group had interrupted the ICIs treatment ($p= 0.12$). Compared with high group, the low group had shown significantly longer OS (29.8 vs 18.5 months, $p= 0.0057$) and PFS (9.1 vs 8.3 months, $p= 0.043$). However, participants in the high group had worse liver function and higher tumor burden compared with those in the low group, and the HBV-DNA group was not the independent risk factor for OS or PFS in the multivariable analysis. After included patients from NCT02973685 (n = 278), the HBV reactivation rate was 5.5% and 4.3% in patients treated with or without ICIs (p = 0.43). **Conclusions:** High HBV-DNA did not significantly increase the incidence of HBV reactivation in HCC patients treated with ICIs and concurrent antiviral prophylaxis. Clinical trial information: NCT04680598. Research Sponsor: None.

Comparative analysis of ctDNA-MRD and MVI in predicting postoperative recurrence of hepatocellular carcinoma.

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Background: Microvascular invasion (MVI) is currently recognized as a pathological feature strongly associated with HCC recurrence. However, its predictive performance in clinical practice remains suboptimal. The detection of minimal residual disease (MRD), which has demonstrated significant prognostic value across multiple cancer types, represents a promising alternative. Therefore, the first goal of this study is to detail the genomic alterations that potentially drive MVI or MRD, the second goal aims to compare their predictive power for postoperative recurrence in early-stage HCC patients. **Methods:** This study profiles the genomic landscape of tumor samples from 126 BCLC 0/A/B stage HCC patients using WES. Patients' longitudinal MRD status was determined through ctDNA detection in peripheral blood at preoperative, 1-, 4-, and 7-month postoperative time points using a tumor-agnostic fixed panel. Postoperative recurrence, confirmed by radiographic imaging, served as the endpoint events for comparing the sensitivity and specificity of two prediction models, with one model based on MVI classification and the other on longitudinal MRD positivity. More patients are currently being recruited and analyzed. **Results:** Among 126 enrolled HCC patients, 71 (56.3%) were classified as MVI-positive (M1/M2), while 55 (43.7%) were MVI-negative (M0). Of the 121 patients with at least one MRD test, longitudinal MRD positivity was observed in 27 patients (22.3%), with 94 patients (77.7%) remaining negative. Both MVI positivity and longitudinal MRD positivity were associated with postoperative recurrence, with longitudinal MRD group showing stronger statistical significance ($p < 0.001$ vs. $p = 0.032$). However, no distinct high-frequency mutation patterns were observed within either the MVI or longitudinal MRD groups. The most frequently altered genes in both groups included TP53, CTNNB1, JAK1, ARID1A, CDKN2A, and AXIN1. Of note, we also developed two prediction models based on MVI classification and longitudinal MRD positivity. The longitudinal MRD-based model demonstrated superior performance, with higher AUROC (0.835 vs. 0.715), PPV (0.357 vs. 0.162), accuracy (0.836 vs. 0.512), and TPR (0.833 vs. 0.786). **Conclusions:** Longitudinal MRD monitoring using a tumor-agnostic fixed panel demonstrates superior predictive performance over MVI classification for postoperative HCC recurrence with higher sensitivity, specificity, and accuracy. The findings highlight the potential of longitudinal MRD monitoring as a more reliable tool for guiding personalized postoperative management in early-stage HCC patients.Moreover, the combination of the two models may potentially offer superior predictive performance for recurrence, which is also a promising direction worthy of further exploration. Research Sponsor: None.

Real-world analysis of ctDNA and other biomarkers in patients with curatively resected stage I-III biliary tract cancer.

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Background: Growing evidence supports the prognostic and predictive value of circulating tumor DNA (ctDNA) detection in gastrointestinal cancers. Building on previous work that demonstrated the feasibility of tumor-informed ctDNA testing in biliary tract cancer (BTC), this study aimed to evaluate ctDNA as a tool for detecting molecular residual disease (MRD) following curative resection and monitor recurrence during surveillance. **Methods:** A retrospective analysis of real-world data was performed on patients (N=171) with stage I-III resectable BTC who underwent ctDNA analysis using a personalized, tumor-informed 16-plex mPCR-NGS assay (Signatera; Natera, Inc.) from July 2020-February 2024. Plasma samples (n=769) were collected pre-operatively, postsurgically (within 2 to 12-weeks; MRD window), and longitudinally until death or last follow-up (surveillance window). The prognostic value of ctDNA was compared to traditional biomarkers such as CA19-9 and CEA. **Results:** A total of 171 patients with stage I-III BTC with a median age of 68 years (range 27-92) were included in this analysis. The median follow-up was 21 months (range: 2-97 months). ctDNA detection rates during the MRD and surveillance windows were 22% (18/83) and 32% (35/109), respectively. On evaluating clinical outcomes, ctDNA-positivity during MRD and surveillance was significantly associated with inferior disease-free survival (DFS) and overall survival (OS). Multivariate analysis confirmed ctDNA-positivity to be the most significant prognostic factor associated with DFS (HR: 10.91, 95%CI: 3.85-30.9, P<0.001) when adjusted for other clinicopathologic factors such as BTC subtype or tumor grade. Additionally, other biomarkers such as CA 19-9 and CEA did not predict clinical outcomes at either the MRD or surveillance windows (Table). **Conclusions:** The data show that ctDNA-positivity was associated with poor DFS and OS, both in the post-op and surveillance settings and that ctDNA detection using a personalized, mPCR-NGS assay was superior to current clinical biomarkers. These findings highlight the value of ctDNA monitoring to improve prognostication in BTC. Research Sponsor: None.

Association of biomarkers with clinical outcomes.

Biomarker	MRD	Surveillance
ctDNA	n= 83	n= 109
DFS	HR: 13.0, p < 0.001	HR: 6.1, p < 0.001
OS	HR: 12.0, p < 0.001	HR: 17.8, p = 0.008
CA19-9	n= 53	n= 80
DFS	HR: 0.88, p =0.81	HR: 1.3, p = 0.51
OS	HR: 1.9, p = 0.389	HR: 10.1, p = 0.045
CEA	n= 18	n= 18
DFS	HR: 0.84, p = 0.85	HR: 0.54, p = 0.5
OS	HR: 1.7, p = 0.71	HR: Not evaluable

4131 Poster Session

Integration of cfDNA fragmentomics for early biliary tract cancer detection.

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Background: Biliary Tract Cancer (BTC) is a highly aggressive malignancy with poor survival outcomes, primarily due to the lack of effective early detection methods and late-stage diagnoses. Current diagnostic tools, including imaging and invasive endoscopic procedures, are limited in their sensitivity and specificity for identifying early-stage disease. This study addresses this critical gap by developing a novel, non-invasive approach for BTC detection using circulating cell-free DNA (cfDNA) fragmentomics features. **Methods:** The study cohort included 163 patients diagnosed with BTC and 165 healthy individuals, divided equally into training and validation cohorts. All participants' plasma samples were collected for a low-depth whole genome sequencing (WGS) process to extract three key cfDNA fragmentomics features: Copy Number Variation (CNV), Fragment Size Distribution (FSD), and Promoter Fragmentation Entropy (PFE). These features were utilized to develop a machine learning model, which was trained and validated through 5-fold cross-validation. An external cohort of 55 patients with benign diseases and 18 Tis/High-grade cases was used to further evaluate the model robustness. **Results:** The stacked ensemble model reached an Area Under the Curve (AUC) of 0.96 in the validation cohort, showing excellent performance in identifying BTC from healthy participants. At an 86% training specificity cutoff, sensitivity achieved 90.91% (95% CI: 81.26% - 96.59%) and specificity 87.88% (95% CI: 77.51% - 94.62%). While PFE performed as a strong single feature with an AUC exceeding 0.92. The model demonstrated its effectiveness in early-stage detection, with the sensitivity increasing from 80% in stage I to 95.65% in stage II. The model surpassed traditional biomarkers (AUC $>$ 95% compared to ~75% for CA19-9) and demonstrated consistent performance across subgroups. External validation revealed 89% sensitivity for early lesions and 89% specificity for benign cases, highlighting its potential for non-invasive early detection of BTC. **Conclusions:** This study demonstrates a reliable and non-invasive strategy for early BTC detection, leveraging cfDNA fragmentomics features and a robust machine learning framework. The model's high accuracy and reproducibility in both internal and external cohorts highlight its potential for clinical implementation, offering a transformative approach for BTC screening. Early diagnosis enabled by this method may significantly improve patient outcomes and survival rates, marking a major advancement in clinical practice. Research Sponsor: Natural Science Foundation of Shanghai; 23ZR1459100, 22ZR1457900; National Natural Science Foundation of China; 82272772,82372832, 82273289; Key Discipline Construction Project of Medicine in Shanghai Xuhui District; SHXHZDXK202304; Research Projects from the Science and Technology Commission of Shanghai Municipality; Grants 21JC1401202; Fujian Provincial Natural Science Foundation of China; 2022J05328.

ADJUBIL: A phase II study of immunotherapy with durvalumab and tremelimumab in combination with capecitabine or without capecitabine in adjuvant situation for biliary tract cancer—The IKF/AIO-ADJUBIL trial.

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Background: Patients (pts) with biliary tract cancer (BTC) still have a poor outcome with limited effective treatment options (only 20% of pts eligible for surgically curative resection, 5-year OS rates $< 10\%$). SOC for BTC is treatment with capecitabine according to the UK BILCAP trial, even though it was formally negative. Based on positive data (TOPAZ-1 and MediTreme trial in BTC, HIMALAYA trial for the STRIDE regimen in HCC), IO combination in the adjuvant setting seems promising. In preclinical studies – particularly in cholangiocarcinoma (CC) –antibody combinations showed stronger and more durable anti-tumor effects than monotherapy, due to synergistic impact on the tumor's immunosuppressive microenvironment. The ADJUBIL trial aimed at evaluating the clinical activity of the anti-PD-L1 antibody durvalumab and the anti-CTLA-4 antibody tremelimumab with or w/o capecitabine in pts with resectable BTC in the adjuvant setting in a pick-the-winner design. The winner of ADJUBIL could be tested in a follow-up phase 2/3 trial against the current SOC capecitabine. **Methods:** In the open-label, multicenter phase II ADJUBIL trial treatment-naïve pts with BTC after curative surgery (R0/R1) were randomized (1:1) to receive either tremelimumab (300 mg, once on D1, cycle 1) plus durvalumab (1500 mg, Q4W; max. 12 months), with (arm A) or w/o (arm B) capecitabine (1250 mg/m2 twice a day on day 1 – 14, Q3W; max. 8 cycles). Primary endpoint was recurrence-free survival at 12 months (RFS@12). The trial design is based on the Simon, Wittes and Ellenberg's Pick-the-winner design [Simon et al., 1985]. **Results:** 40 pts (ECOG 0 or 1) were enrolled in 12 centers in Germany: median age of 64.5 years; 53% males, 30% intra-hepatic CC, 58% extra-hepatic CC, 13% gallbladder. All pts received at least 1 dose of study treatment. The median number of cycles was 7. RFS@12 was 52.4% for arm A and 57.9% for arm B. After a median follow up of 13.8 months, median recurrence free survival was 14.98 (A) and 17.02 months (B). 1y OS rate was 85% (A) and 84% (B). While no new safety/toxicity signs were observed, arm A demonstrated a higher toxicity rate than arm B: 67% of pts having at least one grade ≥ 3 AE (A) vs. 53% (B) and 48% of pts having at least one grade ≥ 3 treatment related AE (A) vs. 32% (B). **Conclusions:** In the IKF/AIO-ADJUBIL trial, the expected RFS@12 of 56% was demonstrated for the combination of durvalumab / tremelimumab without capecitabine (57.9%), whereas no benefit in terms of RSF@12 was observed with additional capecitabine (52.4%). Together with similar 1y OS rates of 85% (A) and 84% (B) and higher toxicity rates in arm A, this indicates superiority of the combination of durvalumab / tremelimumab without capecitabine in pts with resectable BTC in the adjuvant setting. Clinical trial information: EU CT No.: 2024-511847-24-00. Research Sponsor: AstraZeneca.

Novel early-detection model based on cfDNA methylation and fragmentation features for liver cancer.

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Background: In China, the 5-year survival rate of liver cancer patients is only 14%, far lower than the average of 43.7% for all cancer types. Early diagnosis and treatment are essential for survival. Traditional screening methods like AFP combined with abdominal ultrasound have low sensitivity. Recent studies suggest that blood cell-free DNA (cfDNA) characteristics could be a new screening approach for liver cancer. This study aims to compare methylation and fragmentation signals among liver cancer, hepatitis, cirrhosis patients, and healthy individuals, innovatively using these signals to construct an early-detection model which could improve patient prognosis. **Methods:** From July 2023 to November 2024, 315 blood samples were prospectively collected from five Chinese hospitals. The sample set included 105 liver cancer patients and 210 non-liver cancer controls (33 hepatitis, 30 cirrhosis, 147 healthy). This multi-center, multi-disease-controlled collection provides a robust data basis. Targeted enzymatic methyl sequencing detected over 600,000 methylation sites, enabling precise exploration of liver-cancer-related methylation. Beyond methylation, novel fragmentation features like break-point motifs, end motifs, arm-level count, fragment-size distribution and ratio were obtained. These, combined with methylation data, offer a multi-dimensional view for studying liver cancer pathogenesis and biomarkers. A gradient-boosted tree model, integrating 3840 methylation DMR features and fragmentomic model-predicted probabilities, was built. A nested cross-validation framework was used to optimize the model and ensure result accuracy. **Results:** The model achieved a high AUC of 0.97(95%CI:0.95-0.99) in liver cancer detection. At 96.2% specificity, the model had a 91.4% sensitivity for overall liver cancer detection, with 83.7% and 95.8% sensitivity for stage I and II respectively. Among 63 patients with hepatitis or cirrhosis, the model accurately predicted negative results in 88.9% of patients. Notably, for patients hard to identify by traditional tumor markers like AFP and DCP, the model showed high detection rates. When AFP $<$ 400 ng/ml, the detection rate was 88.9%, and with concurrent DCP $<$ 40 ng/ml, it reached 87.0%. When AFP $<$ 20 ng/ml, the detection rate was 89.5%, and with DCP $<$ 40 ng/ml simultaneously, the detection rate was 83.3%. **Conclusions:** This study established an early-detection model for liver cancer by leveraging cfDNA methylation and fragmentation signals. The model demonstrated remarkable performance, particularly in detecting liver cancer patients who are difficult to identify through conventional methods. It blazes a new trail for the early detection of liver cancer and could significantly enhance patient prognosis. Research Sponsor: None.

The efficacy and safety of donafenib as postoperative adjuvant therapy in patients at high risk of recurrence following radical resection of hepatocellular carcinoma (HCC): A multicenter retrospective study.

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Background: Hepatectomy is a crucial treatment for long-term survival in patients with HCC; however, the high recurrence rate significantly impacts prognosis. Currently, there is no standard adjuvant therapy for this patient population. This study investigates the efficacy and safety of Donafenib as postoperative adjuvant therapy for patients with a high risk of recurrence after radical resection of HCC. **Methods:** We analyzed the clinicopathological data of HCC patients with a high risk of recurrence after radical resection, recruited from six medical centers between June 2021 and October 2024. High risk was defined by the presence of any of the following criteria: [i] tumor diameter $>$ 5 cm; [ii] multiple lesions of any size; [iii] microvascular invasion (MVI) grade 1 or 2; [iv] lesions complicated by tumor thrombus (TT); and [v] alpha-fetoprotein (AFP)$\geq$200 μg/L. Patients received either Donafenib monotherapy (D) or combination regimens (D+TACE-DT, D+ICI-DI, or D+TACE+ICI-DTI) as adjuvant therapy. We examined the relapse-free survival (RFS), overall survival (OS), and safety according to CTCAE 5.0. **Results:** 199 patients were included in this study, with a median age of 60 years (IQR: 53-67) at the data cut-off in January 2025. The cohort comprised 85.7% males, 83.4% with HBV infection, 87.9% with Child-Pugh A, and 79.4% with ECOG PS 0. Among patients at high risk, 52.3% had multiple high-risk factors, 53.3% had tumors $>$ 5 cm, 27.1% had multiple lesions, 53.3% had MVI grade 1 or 2, 13.6% had TT, and 36.7% had AFP$\geq$200 μg/L. Treatment distribution included 70 patients receiving D therapy, 69 receiving DT therapy, 46 receiving DI therapy, and 14 receiving DTI therapy. At the data cut-off, the median RFS for the overall population was 27.8 months (95%CI:22.3 months -NE), with a one-year RFS rate of 72.9% (95%CI:66.0%-80.5%) and two-years RFS rate of 55.4% (95%CI: 45.6%-67.2%). In subpopulations based on treatment regimens (D, DT, DI, DTI), the median RFS was 24.5 months (95%CI:20.6 months -NE), 29.2 months (95%CI:22.3 months -NE), 30.0 months (95%CI:19.0 months -NE), and 20.5 months (95%CI:9.3 months -NE), respectively. The median OS for the overall population and subpopulations had not yet been achieved. Among the overall population, 114 patients (57.3%) experienced treatment-related adverse events (TRAE) of any grade, with an incidence of grade 3 TRAE at 8.0% concluding with rash (5.5%), hand-foot syndrome (2.0%) and thrombocytopenia (0.5%); no patients experienced grade 4 or 5 TRAE. **Conclusions:** These preliminary results showed that donafenib as postoperative adjuvant therapy may effectively reduce the recurrence rate in patients at high risk of recurrence following radical resection of HCC, demonstrating good safety and tolerability. Research Sponsor: None.

Effect of the combination of systemic and locoregional therapy on tumor recurrence and survival after liver transplantation for hepatocellular carcinoma (HCC).

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Background: Liver Transplantation (LT) results in the best survival in select HCC patients. Patients that do not meet transplant criteria based on tumor burden may require bridging therapies to downstage their disease to become eligible for LT. There is limited data on safety and efficacy of combining systemic therapy with locoregional therapy (LRT) prior to LT. **Methods:** This study was a single-center retrospective outcome analysis of all patients diagnosed with HCC who underwent LT between June 2018 and March 2024 ($n = 104$) with primary endpoints being 1-year post-LT survival and post-LT tumor recurrence. Explant pathology was also examined to assess tumor necrosis, viability, grade, and lymphovascular invasion. Patients were categorized into 2 groups: 1) LRT alone and 2) combination of LRT and systemic therapy. LRT included Transarterial chemoembolization, Radioembolization, Microwave Ablation, and Stereotactic Beam Radiation Therapy. Systemic therapies included Nivolumab + Ipilimumab, Atezolizumab + Bevacizumab, Sorafenib, Lenvatinib, Ramuricumab, and Cabozantinib. Pearson correlation analysis was used. **Results:** 89 patients received LRT alone and 15 patients received combination therapy. The median maximum tumor diameter in the LRT group was 2.4 cm and that of the combination group was 2.5 cm ($p = 0.136$). Patients in the combination therapy group also had a 3.5-fold increase in the average number of tumors, suggesting higher tumor burden. Average time to post-LT tumor recurrence was similar in combination therapy vs. LRT group (496.8 days vs. 546 days; $p = 0.41$). Patients receiving combination therapy had a trend towards better survival however this did not achieve statistical significance ($r = 0.13$, $p = 0.175$). A statistically significant negative correlation existed between not meeting Milan criteria at the time of transplant evaluation and post-transplant tumor recurrence (i.e., rate of post-transplant tumor recurrence increased if the Milan criteria were not satisfied; $r = -0.31$, $p < 0.001$). **Conclusions:** Our results show that combination therapy using systemic options in addition to LRT is an effective downstaging strategy for high-risk HCC patients and may improve post-transplant survival and reduce post-LT tumor recurrence. This preliminary data suggests that combination therapy may have a favorable impact on the time to post-LT tumor recurrence in patients with higher risk tumors. This further attests the strong need for sustainable downstaging pre transplantation. Using the synergistic effect of these modalities may help expand the pool of candidates who can undergo LT, which remains the most effective long term therapy for patients with HCC. We did not find any evidence of increased rejection or opportunistic infections post LT in the combination therapy cohort. Research Sponsor: None.

Ultra-sensitive detection of hepatocellular carcinoma (HCC) with methylation signal enrichment of ctDNA and hepatitis B virus (HBV).

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Background: Aberrant methylation patterns in cell-free DNA (cfDNA) have been identified as effective biomarkers for HCC early detection, with circulating tumor DNA (ctDNA) from HCC patients exhibiting distinct methylation signatures. Additionally, HBV infection and the associated methylation alterations are closely linked to the development and progression of both cirrhosis and HCC. In this study, we utilize an ultra-sensitive Methylation Anchor Probe for Low Signal Enrichment (MAPLE) to enrich HCC-related methylation signals in ctDNA, as well as those from HBV genomes. By integrating these signals with a machine learning model, we achieve improved discrimination between HCC patients and non-cancer controls, while reducing false positives in individuals with cirrhosis. **Methods:** Whole blood samples were collected from 246 participants, including 96 HCC patients, 123 healthy controls, and 27 cirrhosis individuals. cfDNA was extracted from plasma, followed by enzymatic conversion and library preparation. Targeted hybrid capture was performed using a custom-designed panel that enriched methylation signals associated with HCC and HBV CpG islands. The final libraries were sequenced using next-generation sequencing (NGS). A machine learning model was developed, incorporating methylation features derived from both the human genomic regions and HBV CpG islands. Participants were randomly divided into training and test sets at a 3:1 ratio, with the training set undergoing 5-fold cross-validation for model optimization. To assess model robustness, 40 resampling iterations were conducted to evaluate performance in distinguishing HCC patients across various stages from non-cancer individuals. **Results:** Among all participants, 39.8% tested positive for HBV. Incorporating methylation features from the HBV genome into the model improved sensitivity for detecting early-stage HCC in HBV-positive individuals and enhanced accuracy in distinguishing early-stage HCC from cirrhosis. Analysis of selected HBV methylation features revealed hypermethylation in HCC patients compared to individuals with cirrhosis and healthy controls. The final machine learning model achieved a specificity of 97.6% (96.2%–97.9%). Sensitivities for detecting HCC across all stages were: I: 76.4% (73.5%–79.4%), II: 94.6% (92.0%–97.3%), III: 99.5% (98.8%–100.0%), and IV: 100.0% (100.0%–100.0%). For distinguishing cirrhosis, the model demonstrated a specificity of 81.9% (77.6%–86.3%). **Conclusions:** Using the ultra-sensitive MAPLE technique, we developed a novel panel that enriches methylation signals from both the human and HBV genomes. This assay significantly improved sensitivity for detecting early-stage HCC. By incorporating HBV genome features, we further enhanced the accuracy of distinguishing early-stage HCC from cirrhosis in HBV-positive individuals. Research Sponsor: Shanghai Xiaohe Medical Laboratory Co., Ltd.

Use of artificial intelligence-powered spatial analysis of tumor microenvironment to predict the prognosis in resected gallbladder cancer.

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Background: Gallbladder cancer (GBC) is a highly lethal disease with a lack of reliable biomarkers. The tumor microenvironment (TME) is closely associated with prognosis, but its clinical application as a prognostic marker is limited by evaluation challenges. This study assessed the prognostic significance of AI-powered TME analysis in resected GBC patients. **Methods:** A total of 225 GBC patients with an R0 resection were enrolled, and their hematoxylin & eosin (H&E)-stained GBC sections were analyzed using Lunit SCOPE IO, an artificial intelligence (AI)-powered whole-slide image (WSI) analyze, to evaluate TME-related features, including tumor-infiltrating lymphocyte (TIL) density, fibroblast (FB) density, and tertiary lymphoid structure (TLS) counts. Risk stratification was based on TME-related risk factors (low TIL, high FB, low TLS), and survival outcomes were assessed. External validation was conducted using 146 biliary tract cancer patients. **Results:** Overall survival (OS) and disease-free survival (DFS) declined as the number of TME-related risk factors increased. Patients with three risk factors had the poorest outcomes (median OS: 17.7 months [reference]; median DFS: 12.7 months [reference]), followed by those with two risk factors (median OS: 115.9 months, HR = 0.40, 95% CI: 0.19–0.85; median DFS: 57.8 months, HR = 0.37, 95% CI: 0.18–0.74) and one risk factor (median OS: 126.5 months, HR = 0.34, 95% CI: 0.16–0.74; median DFS: 117.2 months, HR = 0.30, 95% CI: 0.15–0.62). Patients with no risk factors had the best survival (median OS: not reached, HR = 0.20, 95% CI: 0.06–0.67; median DFS: not reached, HR = 0.13, 95% CI: 0.04–0.41). External validation confirmed consistent trends across all risk groups. **Conclusions:** AI-powered TME analysis shows promise as a practical tool for identifying TME-related risk factors using H&E-stained WSI, providing valuable prognostic information for resected GBC patients. Research Sponsor: None.

Unveiling the role of sodium glucose cotransporter-2 inhibitors in hepatocellular carcinoma patients with cirrhosis: A comparative global cohort study.

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Background: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality worldwide, and is often associated with chronic liver disease and cirrhosis. Despite advancements in therapeutic options, the prognosis for HCC patients remains poor. Sodium-glucose cotransporter 2 inhibitors (SGLT2i) exhibit anti-inflammatory, anti-fibrotic, and anti-carcinogenic properties, potentially influencing cancer biology via metabolic and oxidative stress modulation. Our study aimed to evaluate the impact of SGLT2i on outcomes of HCC patients with underlying cirrhosis using a large global database. **Methods:** We conducted a retrospective, propensity score-matched cohort study using TriNetX Analytics Network database. We compared patients aged $>$ 18 years with HCC and cirrhosis who received SGLT2i to those who did not receive SGLT2i from 1/1/2014 to 1/1/2023 for one year. The study cohort included 1,254 cirrhotic HCC patients on SGLT2i, while the control cohort comprised 40,820 cirrhotic HCC patients not on SGLT2i. Propensity score matching was applied to balance demographics, HCC-directed therapies, comorbidities, laboratory values, and medications. Kaplan-Meier analysis estimated event-free survival and overall survival, with comparisons using log-rank tests. The primary outcomes were all-cause mortality, venous thromboembolism (VTE), and all-cause hospitalization rates. Secondary outcomes included all-cause ICU admissions, ischemic stroke/TIA, acute kidney injury (AKI), and septic shock. **Results:** Propensity score matching adjusted for key characteristics resulted in 1,020 matched pairs for each cohort. Our comparative analysis showed that the SGLT2i group had significantly lower all-cause mortality, with a hazard ratio (HR) of 0.399 (95% confidence interval [CI] 0.314, 0.507). Specific outcomes associated with improvement in the SGLT2i group: VTE (HR 0.607, 95% CI 0.481, 0.765), all-cause hospitalization rates (HR 0.568, 95% CI 0.501, 0.644), all-cause ICU admissions (HR 0.522, 95% CI 0.396, 0.689), ischemic stroke/TIA (HR 0.585, 95% CI 0.389, 0.878), thrombocytopenia (HR 0.578, 95% CI 0.470, 0.711), AKI (HR 0.708, 95% CI 0.588, 0.852), and septic shock (HR 0.528, 95% CI 0.382, 0.728). **Conclusions:** Our study highlights the association of SGLT2i with significant improvements in clinical outcomes for HCC patients with cirrhosis. SGLT2i use was linked to reduced all-cause mortality, VTE, hospitalizations, ICU admissions, and complications such as ischemic stroke/TIA, thrombocytopenia, AKI, and septic shock. These findings suggest SGLT2i may offer therapeutic benefits beyond their cardiovascular and renal effects, potentially influencing cancer biology and systemic complications in this high-risk population. Prospective trials are warranted to validate these findings and assess their safety and efficacy. Research Sponsor: None.

Neoadjuvant transhepatic arterial infusion chemotherapy (HAIC) with FOLFOX regime plus cadonilimab (PD-1/CTLA-4 bispecific antibody) for resectable multinodular CNLC Ib/IIa hepatocellular carcinoma (CAR_Hero study).

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Background: The recurrence rate of hepatocellular carcinoma (HCC) remains high, with multinodular HCC being a well-defined high-risk factor for recurrence. However, standardized neoadjuvant or adjuvant therapies for HCC have yet to be definitively established to effectively improve survival outcomes. **Methods:** In this ongoing single-center, phase 2, open-label, prospective cohort clinical trial, eligible pts were randomly assigned (1:1:1) to three arms (15 pts per arm). Neoadjuvant therapies included: (A) 2 cycles cadonilimab (6mg/kg Q2W); (B) once FOLFOX- HAIC and 2 cycles cadonilimab; (C) once FOLFOX-HAIC. Pts receive scheduled surgery on day 21-28 and postoperative adjuvant HAIC one month after surgery. The primary endpoints were major pathologic response (MPR, defined as ≤50% residual living tumor) and the 1-year recurrence-free survival (RFS) rate. Secondary endpoints included overall response rate (ORR, assessed per RECIST 1.1) and treatment-related adverse events (TRAEs). Additionally, a direct hepatectomy cohort was retrospectively collected as reference data. **Results:** A total of 42 pts were enrolled. Among them, 2 pts withdrew due to their desire to pursue conversion therapy. 38 pts underwent hepatectomy and were included in the efficacy analyses (A: 14pts, B: 14pts, C: 12pts). The median age was 55 years (range: 32-72), with 90.5% being male and 90.5% infected with hepatitis B virus. Arm B had the highest MPR rate of 78.6%, significantly higher than Arms A (35.7%) and C (20.0%) (P = 0.011). Additionally, Arm B had the highest ORR (A: 14.3%; B: 40.0%; C: 8.3%), and lowest MVI detection rate (A: 50.0%; B: 21.4%; C: 40.0%). Focal heterogeneity was partially observed. The DCR was 100%. The most common TRAEs were elevated aspartate transaminase (64.3%) and alanine aminotransferase (59.5%). Grade 3-4 TRAEs occurred in 3 pts(hepatic dysfunction and erythema annulare). In Arms A and B, 4 pts experienced a delay in scheduled surgery by 2-4 weeks. The combination of HAIC and cadonilimab did not lead to a significant increase in TRAEs. After propensity score matching, the direct hepatectomy cohort was screened. Kaplan-Meier analysis revealed that the neoadjuvant cohort had a longer recurrence-free survival (RFS) time compared to the direct hepatectomy cohort (median RFS not reached *vs.* 24.7 months; P = 0.0048) and a lower MVI detection rate (36.8% vs. 52.6%). **Conclusions:** Neoadjuvant FOLFOX-HAIC combined with cadonilimab had a considerable antitumor activity, and a manageable safety for the resectable multinodular HCC. It brought the fewer MVIs of tumor and a better RFS. Clinical trial information: ChiCTR3000033692. Research Sponsor: None.

Prognostic significance of pathological response in unresectable hepatocellular carcinoma treated with immune checkpoint inhibitor-based conversion therapy.

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Background: Immune checkpoint inhibitor (ICI)-based conversion treatment is increasingly utilized for patients with initially unresectable hepatocellular carcinoma (HCC). However, standardized histopathologic markers for assessing treatment response and predicting survival outcomes remain inadequately defined. **Methods:** This retrospective study analyzed 225 HCC patients who underwent conversion treatment followed by curative resection. The residual viable tumor percentage (RVT%) was calculated as the proportion of RVT surface area to the total tumor bed area. Kaplan-Meier and Cox regression analyses were used to evaluate the relationship between RVT% and recurrence-free survival (RFS) as well as overall survival (OS). **Results:** Complete pathologic response (CPR), defined as 0% RVT, was achieved in 60 patients (26.7%) and was strongly associated with improved survival outcomes. Patients with CPR exhibited significantly better RFS (HR: 0.23, 95% confidence interval [CI]: 0.13–0.41, $p < 0.001$) and OS (HR: 0.17, 95% CI: 0.05–0.56, $p = 0.003$) compared to non-CPR patients. Multivariate analysis confirmed non-CPR as an independent risk factor for both RFS (HR: 3.67, 95% CI: 1.94–6.96, $p < 0.001$) and OS (HR: 4.43, 95% CI: 1.21–16.18, $p = 0.022$). Major pathologic response (MPR), defined as RVT% $\leq$ 10%, was observed in 91 patients (40.4%) and was also significantly associated with improved RFS and OS (all $p < 0.05$). Stratification by RVT% thresholds revealed a stepwise association between decreasing RVT% and improved survival outcomes. RVT% $\leq$ 30% demonstrated significant predictive power for both RFS (HR: 0.48, 95% CI: 0.30–0.75, $p = 0.001$) and OS (HR: 0.60, 95% CI: 0.31–1.16, $p = 0.020$). Notably, patients with CPR achieved a two-year survival rate of 96.7%, compared to 86.1% in non-CPR patients. Despite the high radiological response rate (CR+PR, 92.4%), substantial discrepancies were observed between radiological and pathological assessments, and 56.7% of patients who achieved pathological complete response (CPR) did not exhibit radiological complete response (CR). Kaplan-Meier analysis showed no significant differences in RFS or OS among three regimens: anti-PD-1 monotherapy (n = 25, 11.1%), anti-PD-1/PD-L1 plus anti-VEGF (n = 21, 9.3%), and anti-PD-1 plus TKI (n = 179, 79.6%). Transarterial chemoembolization (TACE) did not significantly increase the proportion of patients achieving CPR but notably enhanced the proportion of patients with RVT% $\leq$ 30%. **Conclusions:** Both CPR and MPR are robust prognostic markers of RFS and OS in HCC patients undergoing ICI-based conversion treatment. The superior sensitivity of pathological evaluation underscores its advantage over radiological assessment in accurately reflecting treatment outcomes. Research Sponsor: National Natural Science Foundation of China; (82341027 and 82072715).

Comparison outcome of transarterial chemoembolization combined with immune checkpoint inhibitors plus bevacizumab or lenvatinib as first-line therapy for advanced hepatocellular carcinoma.

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Background: Transarterial chemoembolization (TACE) combined with immunotherapy and anti-angiogenic therapy for advanced hepatocellular carcinoma (HCC) presents a promising first-line treatment option. **Methods:** We assessed overall survival (OS), progression-free survival (PFS), objective response rate, and adverse events between the TACE-ICI-Len group (n=160) and the TACE-ICI-Bev group (n=216) as first-line therapy for advanced HCC. Inverse probability of treatment weighting was employed to minimize bias. Efficacy was evaluated using RECIST 1.1 and mRECIST criteria. **Results:** The TACE-ICI-Bev group demonstrated significantly improved OS and PFS compared to the TACE-ICI-Len group, especially across BCLC-B and BCLC-C stages (Total: mOS 22.8 vs. 15.4 months, p<0.001; mPFS 12.4 vs. 8.3 months, p<0.001; BCLC-B: mOS 23.3 vs. 16.6 months, p=0.005; mPFS 14.0 vs. 8.2 months, p<0.0001; BCLC-C: mOS 22.3 vs. 15.1 months, p=0.002; mPFS 11.0 vs. 8.0 months, p<0.001). Within the TACE-Bev-Ate subgroup, OS and PFS were further enhanced (Total: mOS 26.3 months; mPFS 13.8 months; BCLC-B: mOS 27.7 months; mPFS 16.7 months; BCLC-C: mOS 24.2 months; mPFS 12.6 months). The incidence of gastrointestinal bleeding (GB) was significantly higher in the TACE-ICI-Bev group compared to the TACE-ICI-Len group (13.8% vs. 6.2%, p<0.001). Notably, GB was significantly more frequent in patients with portal hypertension (PHT) compared to those without, in both the TACE-ICI-Bev group (30.9% vs. 6.6%, p<0.001) and the TACE-ICI-Len group (20.2% vs. 0%, p<0.001). **Conclusions:** TACE-ICI-Bev demonstrated superior OS and PFS compared to TACE-ICI-Len as first-line treatment for advanced HCC, with an acceptable safety. Management of PHT in patients with advanced HCC is critical to optimizing patient outcomes. Research Sponsor: None.

Patient baseline characteristics before and after applying IPTW.

	Before IPTW			After IPTW		
Variable		TACE-ICI-Bev	TACE-ICI-Len	p	TACE-ICI-Bev	TACE-ICI-Len	p
n		N=216	N=160		N=223.64	N=153.48	
Age (mean (SD))		59.21 (9.81)	57.19 (10.81)	0.059	57.59 (10.00)	57.23 (10.42)	0.780
Sex (%)				0.358			0.784
	Female	37 (17.1)	21 (13.1)		33.1 (14.8)	24.6 (16.0)	
	Male	179 (82.9)	139 (86.9)		190.6 (85.2)	128.9 (84.0)	
Hypertension (%)				0.46			0.928
	No	152 (70.4)	106 (66.2)		150.8 (67.4)	104.3 (67.9)	
	Yes	64 (29.6)	54 (33.8)		72.9 (32.6)	49.2 (32.1)	
DM (%)				0.176			0.981
	No	147 (68.1)	120 (75.0)		164.3 (73.5)	112.5 (73.3)	
	Yes	69 (31.9)	40 (25.0)		59.4 (26.5)	40.9 (26.7)	
ECOG_PS (%)				<0.001			0.888
	0	77 (35.6)	123 (76.9)		123.4 (55.2)	86.1 (56.1)	
	1	139 (64.4)	37 (23.1)		100.2 (44.8)	67.4 (43.9)	
TACE_number (%)				0.011			0.94
	1~2	151 (69.9)	131 (81.9)		169.4 (75.7)	115.6 (75.3)	
	>=3	65 (30.1)	29 (18.1)		54.3 (24.3)	37.9 (24.7)	
Child_Pugh_score (%)				0.125			0.629
	<=6	117 (54.2)	73 (45.6)		109.7 (49.1)	70.6 (46.0)	
	>6	99 (45.8)	87 (54.4)		113.9 (50.9)	82.9 (54.0)	
ALBI_grade (%)				0.367			0.536
	I	94 (43.5)	78 (48.8)		102.7 (45.9)	64.6 (42.1)	
	II-III	122 (56.5)	82 (51.2)		120.9 (54.1)	88.9 (57.9)	
BCLC_stage (%)				0.451			0.51
	B	85 (39.4)	56 (35.0)		82.9 (37.1)	50.9 (33.1)	
	C	131 (60.6)	104 (65.0)		140.7 (62.9)	102.6 (66.9)	
Lymphatic_metastasis (%)				0.001			0.845
	No	126 (58.3)	65 (40.6)		107.1 (47.9)	75.4 (49.1)	
	Yes	90 (41.7)	95 (59.4)		116.6 (52.1)	78.1 (50.9)	
Extrahepatic_metastasis (%)				0.11			0.536
	No	179 (82.9)	121 (75.6)		172.1 (77.0)	123.2 (80.3)	
	Yes	37 (17.1)	39 (24.4)		51.5 (23.0)	30.3 (19.7)	
Ascites (%)				0.298			0.35
	No	146 (67.6)	99 (61.9)		150.5 (67.3)	94.8 (61.8)	
	Yes	70 (32.4)	61 (38.1)		73.1 (32.7)	58.7 (38.2)	
Cirrhosis (%)				0.433			0.47
	No	46 (21.3)	28 (17.5)		40.6 (18.2)	23.4 (15.2)	
	Yes	170 (78.7)	132 (82.5)		183.0 (81.8)	130.1 (84.8)	
PHT (%)				0.425			0.698
	No	106 (49.1)	71 (44.4)		111.6 (49.9)	72.8 (47.4)	
	Yes	110 (50.9)	89 (55.6)		112.1 (50.1)	80.7 (52.6)	
Etiology_(%)				0.113			0.378
	No/other	35(16.2)	16(10)		33.64 (12)	22.18 (14.6)	
	HBV	181(83.8)	144(90)		190 (88)	131 (85.4)	
PVTT_classification_vp (%)				0.367			0.962
	No	122 (56.5)	82 (51.2)		123.2 (55.1)	85.0 (55.4)	
	VP1-VP4	94 (43.5)	78 (48.8)		100.5 (44.9)	68.5 (44.6)	
AFP_400 (%)				0.266			0.979
	<400	119 (55.1)	78 (48.8)		112.8 (50.4)	77.1 (50.3)	
	>=400	97 (44.9)	82 (51.2)		110.9 (49.6)	76.3 (49.7)	
Number_of_tumor (%)				0.979			0.678
	<=3	62 (28.7)	47 (29.4)		66.0 (29.5)	41.7 (27.2)	
	>3	154 (71.3)	113 (70.6)		157.6 (70.5)	111.7 (72.8)	
HCC_diameter_5 (%)				0.823			0.833
	<5	60 (27.8)	47 (29.4)		65.8 (29.4)	47.1 (30.7)	
	>=5	156 (72.2)	113 (70.6)		157.8 (70.6)	106.4 (69.3)	
NLR_grade (%)				0.902			0.884
	<2.81	120 (55.6)	87 (54.4)		126.0 (56.4)	85.1 (55.5)	
	>=2.81	96 (44.4)	73 (45.6)		97.6 (43.6)	68.4 (44.5)	
PLT (%)				0.082			0.901
	<150	122 (56.5)	75 (46.9)		112.7 (50.4)	76.2 (49.6)	
	>=150	94 (43.5)	85 (53.1)		110.9 (49.6)	77.3 (50.4)	

Association of differential expression of genes with survival and relapse in patients treated on the BILCAP clinical trial: Gene expression identification and response to adjuvant chemotherapy in early-stage biliary tract cancer.

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Background: Adjuvant capecitabine is standard of care based on the results of the BILCAP clinical trial, comparing adjuvant capecitabine with observation for early-stage biliary tract cancer (BTC). Translational work on data from BILCAP aims to identify differentially expressed genes in patients whose tumours relapsed or who died from their cancer, as there are currently no validated biomarkers to predict the risk of relapse or death or response to adjuvant chemotherapy in early-stage BTC. **Methods:** Bulk RNA sequencing (RNAseq) was performed on archived fixed formalin samples from consented BILCAP patients. Extracted RNAseq data was quantified using salmon, before undergoing differential gene expression (DGE) using DESeq2 to identify differentially expressed genes in patients who died or whose tumours relapsed, compared to those or survived or had no relapse, accounting for batch effect, different anatomical subtypes and adjuvant treatment. Tumour anatomical subtype was highly associated ($p < 0.05$) with PC2 during principal component analysis and was included as a co-variate during analysis. **Results:** 200 patient samples were analysed; 104 / 200 (52%) patients received chemotherapy while 96 had observation. 142 / 200 (71%) tumours relapsed and 142 / 200 (71%) patients died by the time of data cut off. DGE analysis identified 146 significantly ($p < 0.01$) upregulated genes in patients who died, including PRSS2, AMY2A, SPINK1, CTRC and CELA2A, with significantly ($p < 0.01$) downregulated genes including HP, PHF14, FLI1, NAV3 and NOVA1. 118 genes were significantly ($p < 0.01$) upregulated through DGE analysis in patients died or relapsed, including PAX5, FAM188B, NET1, DEK and WDR1 with significantly ($p < 0.01$) downregulated genes including RQCD1, CPA1, FLI1, NAV3 and NOVA1. 41 genes were significantly ($p < 0.01$) upregulated in both death and relapse, including PAX5, TLK1, ALB, HEATR3 and RAB11-FIP4. 171 genes were significantly ($p < 0.01$) up regulated in patients who died or had their tumours relapse after adjuvant chemotherapy and not in patients undergoing observation, which included THBS1, FAM65B, UBE2W, RPLP0P2 and NPM1, and 66 genes were significantly ($p < 0.01$) downregulated, which included RP11-521B24.3, FLI1, CACNA1A, KCNH6 and MKKS. Gene ontology enrichment analysis identified the upregulated genes as being associated with cytoplasmic translation and the synthesis of both intra- and extracellular RNA and protein complexes. **Conclusions:** Differential gene expression of the BILCAP cohort identified genes associated with cancer relapse and death, including genes associated with a lack of response to adjuvant chemotherapy. Research Sponsor: Incyte.

4143 Poster Session

Comparative analysis of stereotactic body radiotherapy (SBRT) vs. SBRT with bridge therapies for hepatocellular carcinoma patients awaiting liver transplantation: A multi-center study (2010-2020).

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Background: Locoregional therapies, including SBRT, are essential in managing hepatocellular carcinoma (HCC) patients awaiting liver transplantation. This study evaluates outcomes of SBRT alone versus SBRT combined with other bridge therapies over a 5-year follow-up. **Methods:** Data from the TriNetX database (2010–2020) were used to compare two matched cohorts: patients receiving SBRT alone and those receiving SBRT with additional bridge therapies, including transarterial chemoembolization (TACE) and radiofrequency ablation (RFA). Patients included were those meeting liver transplant criteria and classified as AJCC Stage I or II. **Results:** Before matching, the cohorts included 185 patients in the SBRT Alone group and 363 in the SBRT with Other Bridge Therapies group, with significant differences in ethnicity (48.11% vs. 57.3%, p=0.0411) and race (40.54% unknown vs. 31.68%, p=0.0393). After matching (153 patients per group), all variables were balanced, including age (69.4 ± 8.58 vs. 69.1 ± 8.09, p=0.9039) and ethnicity (50.98% vs. 45.75%, p=0.3601). Theoverall survival rate at 5-year follow-up was 61.53% in the SBRT alone group and 62.02% in the SBRT with other therapies group. There was no significant difference between the groups (HR: 0.958, p=0.8417). In the secondary analysis. For acute hepatic failure, the risk was 22.73% for SBRT Alone versus 25.64% for SBRT with Other Bridge Therapies (RR: 0.886, 95% CI: 0.413–1.901, p=0.7567). The risk of decompensated liver disease was 37.74% versus 40% (RR: 0.909, 95% CI: 0.593–1.501, p=0.8054). Procedure-related complications occurred in 11.61% of the SBRT Alone group compared to 12.12% in the other group (RR: 0.958, 95% CI: 0.482–1.904, p=0.9016). Portal vein thrombosis was more frequent in the SBRT Alone group at 12% versus 7.87% (RR: 1.524, 95% CI: 0.712–3.262, p=0.2733). The risk of major adverse cardiovascular events (MACEs) was 24.75% versus 22.12% (RR: 1.158, 95% CI: 0.607–2.213, p=0.6558). Finally, kidney outcomes (acute kidney injury, CKD, ESRD) were similar, with risks of 62.75% and 63.40% (RR: 0.99, 95% CI: 0.834–1.175, p=0.9057). These results suggest no statistically significant differences in the risk of adverse outcomes between the two groups. **Conclusions:** SBRT alone and SBRT with bridge therapies provide comparable long-term survival outcomes in HCC patients awaiting liver transplantation, with differences in specific complications warranting further study. Research Sponsor: None.

Impact of radionuclide therapy on survival outcomes for de novo metastatic gastroenteropancreatic neuroendocrine tumors: A population-based cohort study.

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Background: De novo metastatic gastroenteropancreatic neuroendocrine tumors (dmGEP-NETs) are difficult to treat without the option of radical surgery. The aim of this study was to investigate the survival outcomes of radionuclide therapy. **Methods:** Patients diagnosed with dmGEP-NETs from the Surveillance, Epidemiology, and End Results (SEER)-17 registry database (2000–2021) were included in this study. The impact of radionuclide therapy on overall survival (OS) and cancer-specific survival (CSS) was assessed using univariate Kaplan-Meier method and multivariate Cox regression analysis. **Results:** From 2010 to 2021, a total of 9657 patients at diagnosis years with dmGEP-NETs were determined from the SEER database. On the univariate analysis, patients with dmGEP-NETs who received radionuclide therapy significantly obtained better OS (5-year rate: 55.6% vs. 37.9%; $p < 0.001$) and CSS (5-year rate: 58.2% vs. 44.2%; $p < 0.001$) than patients without radionuclide therapy. Finally, the significant clinical factors associated with OS and CSS were included into multivariate Cox regression analysis to investigate the independent prognostic value of radionuclide therapy. The results showed that radionuclide therapy was an independent prognostic factor for OS (hazard ratio [HR], 0.530; 95% confidence interval [CI], 0.348-0.808; p=0.003) and CSS (HR, 0.508; 95%CI, 0.319-0.808; p=0.004) in patients diagnosed with dmGEP-NETs. Besides, radionuclide therapy was associated with better OS ($p < 0.001$) and CSS ($p < 0.001$) compared to beam radiation. **Conclusions:** Radionuclide therapy was associated with improved survival in patients with de novo metastatic gastroenteropancreatic neuroendocrine tumors. Research Sponsor: Research Launch Fund of Southwest Medical University Affiliated Hospital; 24092.

A phase II study of lenvatinib plus everolimus in advanced extra-pancreatic neuroendocrine tumors (epNETs): Updated results and real-world comparison.

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Background: Advanced epNETs are rare malignancies with limited treatment options beyond somatostatin analogs, peptide receptor radionuclide therapy, and Everolimus (E). Preclinical evidence suggests that dual blockade of VEGF and FGF is an effective antiangiogenic strategy and that concomitant inhibition of the mTOR pathway may be further synergistic. Lenvatinib (L), a multi-target tyrosine kinase inhibitor, suppresses VEGFR, FGFR, and other angiogenic pathways, while E targets the mTOR pathway. Their combination may synergistically impair angiogenesis and tumor growth. **Methods:** This open-label, single-center, phase II study evaluated L + E in patients (pts) with advanced, progressive, well-differentiated (a/p w-d) epNETs. The primary endpoint was objective response rate (ORR). Secondary endpoints were progression-free survival (PFS) and safety. Following a 2-stage design with H0: ORR $< 5\%$ and H1: ORR $\geq 20\%$, up to 32 pts were needed for type I & II error = 10%. In a post-hoc analysis, a real-world cohort of 2:1 matched a/p w-d epNET pts receiving E alone served as a historical comparator. Differences in ORR were assessed using univariable and multivariable logistic regression while those in terms of PFS were analyzed with propensity score-based inverse probability of treatment weighting (IPTW)-adjusted Cox proportional hazards regression and Kaplan-Meier method. **Results:** 32 pts were enrolled. The starting dose regimen was L 18 mg + E 5 mg p.o. daily with L being reduced to 14 mg p.o. daily after the first 3 pts experienced Grade 3 adverse events (AEs). Median age was 59 years (range 33 – 76), and 59% were male. Primary tumor sites included small bowel (59%), lung & thymus (16%), unknown (16%), and colorectal (9%) with the majority being G2 (69%). Median number of prior therapies was 2 (range 0 – 3) while 11 pts had carcinoid syndrome. The study met its primary endpoint: L + E achieved an ORR of 43.8% (6.3% unconfirmed), which was significantly higher than that observed with E alone (3.1%; OR 24.50, 95% CI 5.09 – 117.94, $p < 0.001$). This finding was supported by the multivariable analysis (OR 20.43, 95% CI 3.93 – 106.13, $p < 0.001$). After propensity score-based IPTW adjustment, a trend toward longer PFS favoring L + E (16.0 months [95% CI 13.0 – 23.6] *vs* 11.3 months [95% CI 8.6 – 24.3]; HR 0.88 [95% CI 0.51 – 1.52], $p = 0.647$) was observed. On trial, 23 Grade 3 AEs (11 after L dose reduction) were noted with elevated LFTs (8), hypertension (6) and thrombocytopenia (4) being the most frequent while one Grade 4 AE (hypertriglyceridemia) was reported. **Conclusions:** L + E demonstrated markedly superior ORR and a trend toward prolonged PFS compared to E alone with a manageable safety profile. These findings highlight its potential as a therapeutic option for a/p w-d epNETs and warrant further investigation in randomized trials. Clinical trial information: NCT03950609. Research Sponsor: MD Anderson Cancer Center; Jack T. and Lillian S. Clift Fellowship; Eisai Co., Ltd.

Landscape of functional DLL3 expression in gastroenteropancreatic neuroendocrine neoplasms (GEP NENs).

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Background: Delta-like ligand 3 (DLL3) is an emerging target in multiple neuroendocrine cancers including small cell lung cancer but remains underexplored in GEP NENs. With the ongoing development of multiple classes of therapeutics against DLL3, there is a need to understand the landscape of functional DLL3 expression in GEP NENs. **Methods:** DLL3 immunohistochemistry (IHC) was completed on available tumor samples from patients (pts) with GEP poorly differentiated neuroendocrine carcinomas (GEP NECs) and grade 3 well differentiated pancreatic NETs (G3 WD PanNETs) treated between 2018-2024 and a tissue microarray of resected G1-G2 WD PanNETs (185 samples total). DLL3 positivity (+) was defined as $\geq$ 5% weak (1+) IHC staining. H-scores were calculated by combining % of + tumor cells and degree of staining (1, 2, 3+), ranging from 0-300. Correlations between DLL3 status and clinicopathologic features and outcomes were analyzed. Among selected pts with DLL3 IHC+ GEP NENs, DLL3 immunoPET imaging using the diagnostic tracer [^{89}Zr]Zr-DFO-SC16.56 was completed to evaluate functional expression. **Results:** Among GEP NECs overall, 50/69 were DLL3+ (72%; median H-score 50, interquartile range [IQR] 0-160, range 0-300), including 13/16 esophagogastric (median 45), 11/13 pancreatic (median 60), 7/11 hepatobiliary (median 120), 16/26 colorectal (median 32.5), and 3/3 NECs of other/unknown origin (median 60), with DLL3 expression higher in small cell vs large cell histology (median 120 vs 15, P = 0.011). Among GEP NECs, there was no association between DLL3+ and individual genomic alterations, PFS to 1L platinum-based therapy (median 4.6 mo vs 4.7 mo in DLL3-negative [-], P = 0.435), or OS from diagnosis of advanced disease (median 15.5 vs 12.2 mo in DLL3-, P = 0.629). Among WD PanNETs, DLL3 expression was detected in 3/46 (7%) G1, 1/23 (4%) G2, and 19/47 (40%) G3 tumors, with median Ki67 higher among DLL3+ vs DLL3- tumors overall (42% vs 6%, $P <$ 0.001) and within G3 WD PanNETs alone (48% vs 30%, P = 0.009). Among pts with advanced G3 WD PanNETs, DLL3+ was associated with shorter OS from diagnosis of advanced G3 disease (median OS 23.1 mo vs 43.9 mo in DLL3-, P = 0.012). [^{89}Zr]Zr-DFO-SC16.56 DLL3 PET imaging was completed on 5 pts with DLL3 IHC+ GEP NENs at progression on standard systemic therapy. Notably, a pt with pancreatic NEC and liver metastases (DLL3 IHC H-score 60) demonstrated high tumoral tracer uptake (SUV_{max} 36.7) with 95% of tumor lesions demonstrating DLL3 PET avidity. Among 4 pts with DLL3 IHC+ G3 WD PanNETs, DLL3 PET was positive in 3/4, with SUV_{max} ranging from 14.4-27.5 and % of DLL3 PET+ tumor lesions ranging from 50-100%. **Conclusions:** DLL3 is expressed on a majority of GEP NECs and on a minority of well differentiated PanNETs marked by high grade disease and poor clinical outcomes. Functional DLL3 PET imaging highly suggests DLL3 as a promising therapeutic target in both GEP NECs and high grade WD PanNETs. Research Sponsor: Memorial Sloan Kettering Cancer Center.

Surgical debulking versus non-surgical management for the control of carcinoid syndrome in metastatic small bowel neuroendocrine tumors.

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Background: Somatostatin analogues (SSAs) are first-line systemic therapeutics for tumor- and symptoms control in well-differentiated small bowel neuroendocrine tumors (SBNETs) with liver metastases. Surgical debulking of neuroendocrine tumor liver metastases (NETLMs) has historically been associated with symptom control in patients with carcinoid symptoms. Herein, we compare clinical outcomes in patients with metastatic SBNETs treated with surgical debulking for NETLMs to SSA alone or in combination with non-surgical liver directed therapies (LDTs) i.e. bland embolization or radioembolization. **Methods:** Patients with serotonin-producing SBNETs and NETLMs with documented symptoms of carcinoid syndrome were included in this retrospective chart review. Primary outcome was symptom-free-interval (SFI), defined as the time from start of treatment until return/worsening of symptoms. Patients were censored for SFI if a new line of tumor-directed therapy was initiated for radiographic disease progression in the absence of return/worsening of symptoms. Time to event outcomes were analyzed using Kaplan-Meier estimations, log-rank test, and Cox proportional hazards regression model. Medians were compared using the Mann–Whitney U test. **Results:** Between 2018 – 2024, 64 consecutive patients with carcinoid symptoms were included for analysis. 42 patients (65.6%) underwent surgical debulking (SDB) of NETLMs and 22 patients were treated with SSA alone (n = 14) or SSA plus LDT (n = 8). The proportion of patients reporting symptom improvement was not significantly different between the SDB and non-surgical (NS; SSA + LDT) groups (SDB = 38, 90.5% vs. NS = 19, 86.4%; p = 0.68). Among those with symptom improvement (n = 57), SFI was significantly longer in the SDB group (median SFI; SDB = 28.2 months [m] vs. NS = 15.9 m; p = 0.004). Radiographic PFS was also significantly prolonged in the SDB group (SDB = 26.1 m vs. NS = 12 m; HR, 0.53; 95% CI, 0.29 – 0.95; p = 0.03). Within the SDB group, there was no significant difference in SFI between patients who continued to receive SSA post-op (n = 23) and those in whom SSA was discontinued (n = 19) post-op (28 m vs. 30.6 m; p = 0.85). Post-treatment median nadir serotonin was significantly lower in the SDB group (total N = 41 [SDB = 31 + NS = 10]; SDB = 299 ng/mL vs. NS = 947.5 ng/mL; $p < 0.001$). Median percentage decrease (from pre-treatment to nadir values) in serum serotonin was higher in the SDB group with the difference approaching significance (total N = 30 [SDB = 22 + NS = 8]; SDB = 80.9% vs. NS = 51.5%; p = 0.06). **Conclusions:** Despite the frequent use of SSAs, surgical debulking of NETLMs in patients with carcinoid symptoms remains superior for symptom control and should therefore be considered in these patients. Research Sponsor: None.

TROP2 expression in the gastroenteropancreatic neuroendocrine tumors: An analysis of 179 patients.

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Background: Trophoblast cell-surface antigen 2 (TROP2) is a transmembrane glycoprotein that exhibits overexpression in various gastrointestinal (GI) malignancies, including colorectal, gastric, pancreatic, and esophageal cancers. This overexpression has been correlated with increased tumor aggressiveness, enhanced proliferation, and unfavorable prognostic outcomes. TROP2 serves as a predictive and prognostic biomarker in several GI cancers, guiding targeted therapy and correlating with overall survival. However, there exists a notable absence of dedicated studies investigating TROP2 expression specifically in gastroenteropancreatic neuroendocrine tumors (GEP-NETs) highlighting an unmet need. This report presents the first and most extensive prospective study examining TROP2 overexpression in GEP-NETs. **Methods:** We utilized transcriptomic and clinical data derived from the National Cancer Institute's (NCI) GEP-NET project, which originates from a prospective study approved protocol (NCT05237934). For data analysis, we implemented the RNA-sequencing pipeline developed by the NCI Cancer Center Bioinformatics Resource (https://github.com/skchronicles/RNA-seek.git) along with STAR version 2.7.11b for aligning sequencing reads to the hg38 reference genome. To accommodate the variations introduced by different library preparation methodologies (including polyA, total RNA, FFPE, and access), we employed the "RemoveBatchEffect" function from the Limma package, while also accounting for disease-specific variations. **Results:** Our analysis included a total of 179 GEP-NET samples, comprised of 106 small bowel neuroendocrine tumors (NETs) and 73 pancreatic neuroendocrine tumors (pNETs). There were 54 females and 52 males in the small bowel cohort, and 37 females and 36 males in the pancreatic cohort. Notably, TROP2 expression was observed in 50% of pancreatic samples and 30% of small bowel NET samples. Furthermore, TROP2 expression appeared to correlate with decreased survival in pNETs (p=0.022), whereas its expression in small bowel NETs may suggest improved patient outcomes, although this latter correlation did not achieve statistical significance (p=0.37). Further analyses are pending study completion and will be presented later. **Conclusions:** This study highlights the critical role of TROP2 overexpression in GEP-NETs and its importance for patient prognosis. TROP2 overexpression correlates with decreased survival outcomes in pNETs relative to small bowel NETs. Additionally, the identification of TROP2 as a prognostic and predictive biomarker presents opportunities for future research focused on therapeutic targeting. Additional studies may be needed for further validation as we finalize the current research. Research Sponsor: None.

Development of a cfDNA-based protein-informed epigenetic signature (PEp-sig) to enable biomarker-based risk stratification for pancreatic ductal adenocarcinoma (PDA).

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Background: Novel blood-based biomarkers are needed for early risk stratification and personalized therapies for patients with PDA. An evidence-based 99-gene panel was developed focusing on genes whose protein products are implicated in PDA drug response. We hypothesized that methylation levels in these genes could serve as surrogates for their corresponding protein activity, enabling the prediction of treatment-related outcomes in PDA patients. Using this panel, we developed a cell-free DNA (cfDNA)-based PEp-sig for risk stratification of patients with PDA. **Methods:** Targeted enzymatic methylation sequencing was performed on plasma samples from PDA patients (01/2010–05/2022) receiving chemotherapy from the Ohio State University biorepository. Gene methylation levels were analyzed for associations with overall survival (OS) using univariate and multivariate Cox regression models. Significant genes and covariates such as first chemotherapy (FLC)- FOLFIRINOX (FFX) vs. gemcitabine (G)/nab-paclitaxel (NP) vs. other (Ot), and stage at diagnosis (StD) – early-stage (ES) that includes resectable and borderline resectable PDA vs. locally advanced (LA) and metastatic (Met)) were identified through backward selection. Risk scores from multivariate models were dichotomized at the median, stratifying patients into High (Hg) and low-risk groups (Lg), with survival differences assessed by Kaplan-Meier and log-rank tests. **Results:** The study cohort (SC) included 51 PDA patients (StD: 22 ES, 15 LA, and 14 Met). Among the ES cases, 3 progressed to Met after neoadjuvant therapy (NAT); in the LA sub-group, 2 proceeded to surgery post-chemotherapy. Ultimately, 21 patients had resection (Rs), while 30 underwent palliative therapy (PT), with FLC distribution as follows: PT group – 12 FFX, 16 G/NP, and 2 Ot; Rs group, NAT—9 FFX, 1 G/NP, and 1 Ot; adjuvant therapy after upfront surgery (UpS) —5 FFX, 2 G/NP, 3 Ot. Two 15-gene PEp-sig were developed: one for the SC and another for the PT group. A significant overlap (11/15) of genes was observed between the two PEp-sigs. These genes are linked to the response to G, NP, irinotecan, and platinums. The performance of PEp-sig models, with and without FLC and StD adjustments, is summarized below. **Conclusions:** In this proof-of-concept study, we present a cfDNA-based PEp-sig that effectively stratifies PDA patients by survival risk. Notably, it operates independently of FLC and StD within the PT group. Ongoing efforts aim to develop treatment selection algorithms based on these findings. Research Sponsor: None.

Models tested	SC			PT-group		
	Hg vs. Lg OS (in months)	Hazard Ratio (HR)	p-value	Hg vs. Lg OS (in months)	HR	p-value
PEp-sig alone	10.75 vs. 33	8.7				
PEp-sig + FLC*	10.62 vs. 33	8.1	<0.001	5.3 vs. 16.83	9.2	<0.001
PEp-sig + StD*	8.4 vs. 33	16.9			8	

**FLC and StD significantly impacted OS in SC but not in PT.*

Development of a comprehensive cfDNA methylation signature for prognostic, predictive, and diagnostic applications in pancreatic ductal adenocarcinoma (PDA).

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Background: Blood-based biomarkers are promising for predicting outcomes in pancreatic ductal adenocarcinoma (PDA) and could pave the way for developing multi-omic prognostic tools. We previously identified a 15-gene cell-free DNA (cfDNA) methylation signature targeting treatment response (TRg). To enhance its utility, we incorporated additional genes with established prognostic (Prg) and diagnostic (Dxg) value from the literature, creating a composite panel. This study aimed to develop a comprehensive cfDNA methylation signature with predictive, prognostic, and diagnostic value. **Methods:** Enzymatic methylation sequencing was performed on plasma samples collected between January 2010 and May 2022 from PDA patients undergoing chemotherapy at The Ohio State University. A 206-gene panel (TRg + Prg + Dxg) was analyzed, with methylation levels correlated to overall survival (OS) using univariate and multivariate (MV) Cox regression models. Backward selection identified significant genes, and MV models adjusted for clinical covariates. Patients were stratified into high-risk (Hg) and low-risk (Lg) groups based on median risk scores. **Results:** Our study cohort had 51 PDA patients, with a median age of 65 (range: 34 -80), 53% females, and 86% Caucasian (12% African-American and 2% others). Stage at diagnosis (Dx-S) distribution: 15 locally advanced (LA), 14 metastatic (Mets), and 22 resectable/borderline resectable (R/BR). 12 patients in BR/R received neoadjuvant therapy (NT) while the rest had upfront surgery (UpS) followed by adjuvant therapy (AT). Ultimately, 21 had resection, and 30 got palliative therapy. First-line chemotherapy (FL) patients received is, 36 FOLFIRINOX (12 PT, 9 NT, and 5 AT), 19 gemcitabine (Gem)/nab-paclitaxel (NP) (16 PT, 1 NT, and 2 AT), and 6 Others. A 25-gene cfDNA methylation signature (15 TRg, 10 Prg, and 1 Dxg) stratified patients into Hg and Lg groups. OS was significantly longer in Lg compared to Hg across all models. **Conclusions:** The study successfully developed a comprehensive 25-gene cfDNA methylation signature combining predictive, prognostic, and diagnostic markers for PDA. This signature effectively stratifies patients into Hg and Lg, demonstrating significant differences in OS across various clinical models. The results highlight the potential utility of cfDNA methylation as a multi-omic tool to enhance personalized treatment strategies and improve patient outcomes in PDA. Further validation in larger cohorts is warranted to confirm its clinical applicability. Research Sponsor: None.

Models tested	OS* Hg vs. Lg	Hazard ratio
Signature-alone	7.58 vs. 33	13.5
Plus, FL	8.98 vs. 33	13.2
Plus, FL, Surgery (NAT vs. UpS vs. PT)	7.58 vs. 33	17.3
Plus, Dx-S	7.58 vs. 33	14.4

*In months.

DNA methylation signatures as predictive biomarkers for chemotherapy (CT) resistance and survival in pancreatic ductal adenocarcinoma (PDA).

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Background: Predicting innate treatment resistance to traditional CT in PDA can optimize therapeutic strategies and improve patient outcomes. This study investigates methylation changes in genes encoding proteins implicated in preclinical models (PDA cell lines or mouse models) influencing drugs commonly used to treat PDA, including 5-fluorouracil (5FU), oxaliplatin, irinotecan, gemcitabine (Gem), nanoliposomal irinotecan, and nab-paclitaxel. Using a comprehensive literature review (1970–2024), we curated a panel of relevant genes and analyzed their methylation patterns in The Cancer Genome Atlas (TCGA) database. We hypothesized that DNA methylation changes affect gene expression and protein production, contributing to chemotherapy resistance. **Methods:** PDA patient methylation data were accessed from the TCGA database. Survival analyses were performed using elastic net multivariate regression to identify significant methylation signatures, followed by Kaplan-Meier analysis. Model parameters, including alpha (α) and lambda (λ), were optimized through 100 iterations to minimize error. Our curated panel consisted of 138 genes, predominantly Gem-specific or Gem + 5FU (n = 93). **Results:** The TCGA database provided methylation data for 184 PDA patients (106 had Gem or Gem-based therapy), with 133/138 genes in our analysis. Our analysis identified 23 cytosines followed by guanine residue (CpG) methylation signatures within the panel, ranging from 1 to 23 CpG sites. The best-performing signature, containing 21 CpG sites, stratified patients into significantly different survival groups (17 months (m) vs. not evaluable, p = 0.004). The second-best signature, with 8 CpG sites, stratified survival as 17m vs. 66.94m (p = 0.03). Interestingly, signatures with the most (n = 23) and least (n = 1) CpG sites also demonstrated strong stratification, with survival differences of 15.15m vs. 30.02m (p = 0.01) and 18.67m vs. 44.38m (p = 0.01), respectively. Many signatures included multiple CpG sites from single genes. A Gem or Gem + 5FU-specific panel (n = 93) applied to patients treated with Gem-based therapy identified an 8-CpG signature distinguishing high-risk patients (20.84m vs. 49.38m, p = 0.02). **Conclusions:** This study highlights the potential of CpG methylation signatures to predict treatment outcomes in PDA. These findings may guide the identification of high-risk patients and the optimization of CT regimens for improved survival. The identification of methylation signatures associated with genes implicated in chemotherapy resistance provides valuable insights into the underlying mechanisms of innate treatment resistance in PDA. Further validation of these methylation signatures could contribute to more effective and targeted therapeutic approaches in clinical practice. Research Sponsor: None.

A phase I trial of binimetinib plus hydroxychloroquine in patients with previously treated metastatic pancreatic cancer.

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Background: Combined MEK and autophagy inhibition exerts synergistic antitumor activity in preclinical models of RAS-mutant cancers. We hypothesized that blockade of autophagy with hydroxychloroquine (HCQ) can overcome therapeutic resistance to MEK inhibition with binimetinib (bini) and lead to clinical benefit in patients (pts) with previously treated, KRAS-mutant metastatic pancreatic ductal adenocarcinoma (PDAC). **Methods:** This is an investigator-led, single-arm, open-label, phase I dose escalation/expansion study of bini + HCQ in metastatic PDAC pts. Key eligibility criteria: ECOG 0-1, adequate organ function, >1 prior line of therapy for metastatic disease, and presence of KRAS mutation. Dose escalation followed a Bayesian optimal interval (BOIN) design. Dose level (DL) 1: bini 45 mg + HCQ 600 mg p.o. bid; DL -1: bini 45 mg + HCQ 400 mg p.o. bid; DL -2: bini 30 mg + HCQ 400 mg p.o. bid; DL -1.5: bini 30 mg + HCQ 600 mg p.o. bid. Primary endpoint was the maximum tolerated dose (MTD) of bini + HCQ. Secondary endpoints included objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS). **Results:** From December 2019 to August 2024, a total of 34 pts were enrolled in dose escalation (n = 17) and dose expansion (n = 17). Median age was 65 yrs (range: 45-79) with 56% females. Median prior lines of therapy was 2 (range: 1-4). The most prevalent KRAS mutation subtypes were G12D (35%), G12V (32%), and G12R (29%). Two dose-limiting toxicities (DLTs) occurred in 2 out 3 pts treated at DL 1: grade 3 CPK elevation with renal impairment (bini) and grade 3 QTc prolongation (HCQ). The most frequent non-hematologic AEs were rash (71%), diarrhea (71%), nausea (67%), elevated AST (67%), and elevated CPK (61%). Following dose de-escalation due to poor tolerance, the MTD was deemed to be bini 30 mg + HCQ 600 mg p.o. bid and used for dose expansion. Overall, out of 31 response-evaluable pts, 2 pts achieved a partial response (lasting 6.9 and 4.7 mos, both at DL -1.5) and 9 pts achieved stable disease (3 pts at DL -1, 6 pts at DL -1.5), consistent with ORR 6.5% and DCR 35.5%, respectively. At median follow-up of 19 mos, median PFS was 1.9 mos and median OS was 5.3 mos. **Conclusions:** Bini + HCQ demonstrated a challenging toxicity profile and limited clinical activity in a heavily pretreated cohort of metastatic PDAC pts. Minimal efficacy was observed in this treatment-refractory population; however, dual MEK and autophagy inhibition may warrant further study in earlier-line settings, potentially with more tolerable drug candidates and guided by biomarker selection. Clinical trial information: NCT04132505. Research Sponsor: None.

Pancreatic adenosquamous carcinoma (PASC): A comparative genomic landscape study.

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Background: PASC accounts for 1-4% of primary exocrine pancreatic malignancies and is associated with more aggressive disease biology and worse clinical outcomes compared to conventional pancreatic ductal adenocarcinoma (PDAC). Despite its aggressive nature, PASC lacks targeted treatment choices and is frequently excluded from clinical trials, underscoring a key unmet need. Here, we performed a comparative analysis of the genomic landscapes of PASC versus PDAC using the FoundationOne database to identify distinct molecular drivers and potential therapeutic targets. **Methods:** Comprehensive genomic profiling using hybrid capture-based next-generation sequencing (NGS) was performed on 244 PASC and 29,021 PDAC tumors to identify genomic alterations (GAs). All patients (pts) had clinically advanced disease, predominantly stage IV, at the time of profiling. Genomic ancestry, MSI status, tumor mutational burden (TMB), homologous recombination deficiency signature (HRDsig) and cosmic trinucleotide signature were assessed. PD-L1 expression was quantified using the tumor proportion score (TPS) via the Dako 22C3 immunohistochemistry assay. Statistical analysis was performed using Fisher's exact test, with false discovery rate (FDR) correction applied through the Benjamini-Hochberg method. **Results:** PASC harbored a median of 6 GAs per tumor (range: 1-23) with a similar genomic ancestry profile compared to PDAC. Of note, PASC featured a higher frequency of cases with MSI-high status (2.1% vs 0.5%; p = .027) and TMB $>$ 10 mutations/Mb (3.7% vs 1.3%; p = .013). Additionally, PD-L1 expression (TPS $>$ 1%) was significantly more common in PASC compared to PDAC (66.7% vs 37.0%; p $<$ .0001). The frequency of *KRAS* mutations and HRDsig positivity was similar between the two subtypes. Disease-associated GAs more frequent in PASC than PDAC included mutations in *CDKN2A* (77.0% vs 56.6%; p $<$ .0001), *KMT2D* (8.2% vs 3.2%; p $<$ .0001), *TP53* (89.3% vs 78.0%; p $<$ .0001), and *MTAP* loss (33.3% vs 23.8%; p = .002). **Conclusions:** PASC exhibits a genomic profile with molecular features that are both shared and distinct compared to PDAC. Given the similar frequency of *KRAS* mutations, PASC pts should be included in clinical trials of emerging RAS-targeted therapies. Furthermore, immunotherapy-based strategies (↑MSI-high, TMB, and PD-L1) and PRMT5/MAT2A inhibitors (↑MTAP loss) warrant consideration in this rare and understudied disease subtype. Research Sponsor: None.

	PDAC (n=29,021)	PASC (n=244)	P-value
Median GAs/tumor (range) (IQR)	5 (0-61) (3-6)	6 (1-23) (4-8)	<.0001
MSI-high	0.5%	2.1%	.027
TMB > 10 muts/Mb	1.3%	3.7%	.013
PD-L1 TPS > 1%	37.0%	66.7%	<.0001
HRDsig+	4.6%	3.1%	NS
CDKN2A	56.6%	77.0%	<.0001
KRAS	92.8%	95.5%	NS
***MTAP* loss**	23.8%	33.2%	.002
TP53	78.0%	89.3%	<.0001

Unveiling the differences in tumor immune microenvironment between *KRAS*-wildtype and *KRAS*-mutant pancreatic ductal adenocarcinoma.

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Background: Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive cancer with a dismal prognosis despite advances in treatment. PDAC is characterized by a dense stromal environment with suppressed anti-tumor immunity that contributes to treatment resistance. Oncogenic *KRAS* mutations are present in $>$ 90% of PDACs and are known to play a role in modulating the tumor immune microenvironment (TME). In this study, we examined the differences in TME components between *KRAS*-mutant (m) and *KRAS*-wildtype (wt) PDACs. **Methods:** Comprehensive genomic and immune profiling (CGIP), including the RNA-seq based gene expression assessment of 395 immune-associated genes, was performed on 311 PDAC patient samples. Gene expression signatures of tumor immunogenicity (TIGS) and cell proliferation were calculated by averaging the gene expression ranks of 161 immune-associated genes and 10 proliferation genes, respectively. The normalized gene expression rank of 22 immune checkpoint genes and 17 cancer testis antigen (CTA) genes were also calculated. DNA-seq was used to identify *KRAS* mutations and to calculated tumor mutational burden (TMB). Continuous variables were compared between subgroups using the Wilcoxon Rank-Sum test and categorical variables were compared between groups using the Chi Squared test. For statistical significance, $p < 0.05$ was required. **Results:** The cohort consisted of 311 PDAC patient samples, comprising 159 females (51.1%) and 152 males (48.9%) with a median age at testing of 69.3 years (38.7-92.6). A total of 264 specimens (84.9%) exhibited a *KRAS* mutation, with the most common being G12D and G12V while 47 (15.1%) had *KRAS*-wt tumors. No difference in TIGS, CP, or TMB was observed between *KRAS*-wt and *KRAS*-m tumors. *KRAS*-wt tumors exhibited greater expression of 12 of 17 tested CTAs than *KRAS*-m tumors, including GAGE13 ($p = 0.004$) NY-ESO-1 ($p = 0.01$), MAGEA3 ($p = 0.01$), and LAGE1A ($p = 0.01$). Analysis of the gene expression of 22 immune checkpoint genes showed no difference for most of the genes, though there was higher expression of PD-1 ($p = 0.04$) and CD27 ($p = 0.03$) seen in *KRAS*-wt compared to *KRAS*-m tumors. **Conclusions:** *KRAS*-wt PDACs exhibited greater expression of cancer testis antigen genes compared to *KRAS*-m tumors, suggesting potential therapeutic susceptibility to immunotherapy and adoptive cell therapies leveraging the expression of CTAs as targets. Assessment of *KRAS* status and immunotherapy susceptibility may support future clinical trial selections for therapies targeting the complex interplay of genomic and immune components of pancreatic cancer. Research Sponsor: None.

Functional role of GLI2 in cancer-associated fibroblasts for modulation of the fibrotic tumor microenvironment within pancreatic cancer.

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Background: The tumor microenvironment (TME) that surrounds pancreatic ductal adenocarcinoma (PDAC) is a multi-faceted and dynamic ecosystem in which stromal fibroblasts communicate with cancer cells to mediate tumor growth, metastasis, and chemotherapy resistance. It is well recognized that both cancer-associated fibroblasts (CAFs) and its non-cellular, fibrotic components within the TME can foster a protumorigenic environment for PDAC. However, we still lack a comprehensive understanding of the precise mechanisms in which this dense, fibrotic matrix can help drive malignant behaviors. Here, we reveal a novel mechanism in which the zinc-finger transcription factor GLI2 regulates type 1 collagen expression within CAFs and how the soluble variant of this collagen promotes irinotecan chemoresistance. **Methods:** We leveraged transcriptomic data from The Cancer Genome Atlas, International Cancer Genome Consortium, and Clinical Proteomic Tumor Analysis Consortium to evaluate GLI2 expression and stromal content of human PDAC tumors through bulk RNA-sequencing deconvolution. Using single-nucleus RNA sequencing of human PDAC tumors, we validated the association of GLI2 expression and stromal matrix constituents in CAFs. Chromatin immunoprecipitation assays in human CAFs confirmed GLI2 binding at the COL1A1 promoter. Through RNAi-based inactivation of GLI2, we determined how loss of GLI2 impacts regulation of type 1 collagen. Additionally, we conducted MTT assays to assess tumor viability in response to irinotecan treatment. **Results:** Transcriptomic analysis revealed that GLI2 is highly enriched in CAFs and strongly correlated with stromal fibrosis compared to other non-tumor cell constituents within the TME. We have shown that GLI2 directly binds to the promoter of COL1A1, a key component of type 1 collagen, in CAFs and regulates its transcription in a manner dependent on TGFβ1 signaling. Interestingly, PDAC tumors exposed to type 1 collagen show increased expression of pro-tumorigenic pathways involved in inflammation, EGR signaling, cytokine-receptor interactions, and irinotecan resistance. We further validate that human PDAC cells pre-treated with collagen can confer chemoresistance to irinotecan with viability assays. **Conclusions:** Taken together, our study demonstrates a novel mechanism in which GLI2 regulates the secretion of collagen within CAFs, which in turn can enable PDAC to acquire resistance to standard-of-care treatments. These findings highlight not only the oncogenic functions for CAFs and their fibrotic secretome, but also open new avenues in which therapeutic targeting of the TME may provide clinical benefit for PDAC patients. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health.

Use of an ultra-sensitive sequencing platform to detect mutant *KRAS* in the whole blood of pancreatic cancer patients.

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Background: Pancreatic Ductal Adenocarcinoma (PDAC) is a leading cause of cancer death and mortality is increasing. A contributor to poor outcomes is the absence of non-invasivebiomarkers for disease screening, treatment monitoring, and identification of therapeutic targets. Blood-based profiling of circulating tumor DNA (ctDNA) using Next Generation Sequencing (NGS) has addressed these needs in several cancer types, but available commercial ctDNA assays are not as effective in PDAC. To address this unmet clinical need, we developed an ultra-sensitive sequencing assay to detect mutant *KRAS* in the whole blood of PDAC patients. **Methods:** We adapted the bacterial Maximum Depth Sequencing (MDS) assay for Human whole blood MDS (hMDS) to improve upon the sensitivity of NGS by barcoding DNA fragments with unique molecular identifiers prior to performing multiple rounds of first-strand synthesis to resolve sequencing errors. Analytic sensitivity was evaluated by spiking PDAC cells at various dilutions into control blood isolated from 10 individuals and assaying the mixture by hMDS in triplicate. Clinical sensitivity was then evaluated by collecting paired blood draws from 200 advanced PDAC patients in prospective fashion, one to be tested with a commercial ctDNA test and one by hMDS. **Results:** ThehMDS assay reproducibly detected PDAC cells at dilutions as low as one cell per mL or one mutated fragment per million *KRAS* fragments. Thus, hMDS reached an analytic sensitivity 1000x higher than NGS. Clonal *KRAS*mutations were detected in 179 of the first 194 patient samples (92.2%), surpassing historical commercial detection rates of 50% by commercial ctDNA assays. Mutations were reproducibly detected in replicate analysis of forward and reverse DNA strands. Weak clonal *KRAS* activating mutations were also detected in several non-cancer, control patients. **Conclusions:** We developed an assay capable of sensitively detecting PDAC ctDNA in whole blood. Formal comparison to commercial testing is ongoing, but preliminary results suggest this assay could be a sensitive tool for non-invasive PDAC mutation profiling and disease monitoring. The presence of weak clonal *KRAS* mutations in control patients has motivated development of a multiplex platform capable of screening for mutations in multiple driver genes. Research Sponsor: National Cancer Institute; 5R21-CA257816-02; Hopper Belmont Foundation.

Efficacy and safety of surufatinib (S) plus KN046 (K) and chemotherapy in first line (1L) advanced pancreatic cancer (PC): A single-arm, phase 1b/2 trial.

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Background: Gemcitabine (G) and nab-paclitaxel (nP) are standard 1L regimen for patients (pts) with unresectable PC, yet the efficacy remains unsatisfactory. K is a humanized bispecific antibody targeting PD-L1/CTLA-4, while S is a kinase inhibitor of VEGFR1-3, FGFR1 and CSF-1R with immune-regulatory potential. It is hypothesized the add-on of S and K to GnP chemotherapy would provide improved efficacy. **Methods:** This single-arm, phase 1b/2 trial enrolled pts with unresectable locally advanced or metastatic PC who were eligible for 1L treatment. The phase 1b part was designed in a "3+3" algorithm to determine the recommended phase 2 dose (RP2D) of S for dose expansion in phase 2 part. Pts received oral S at escalating dose starting from 200 mg qd, plus intravenous K at 5 mg/kg on day 1, and GnP chemotherapy on days 1 and 8 at 21-day cycles. The primary endpoint was dose-limiting toxicities (DLTs) within the first 28 days for phase 1b, and ORR per RECIST 1.1 for phase 2. Secondary endpoints included DCR, PFS, OS, safety, and efficacy-related biomarkers. **Results:** As of Dec 19th, 2024, 18 pts were enrolled with a median age of 54 (range: 41-74), predominantly male (16/18) and metastatic disease (15/18). Of the 16 pts with genetic testing, *KRAS* (15/16) and *TP53* (11/16) mutations were common, followed by DNA damage response (DDR) -related mutations (7/16) including *ARID1A*, *ATM*, *CHEK2*, etc., while TMB-H (1/16) is rare, and none had MSI-H or dMMR status. Within the 9 pts from phase 1b part (3 in S 200 mg cohort, 6 in S 250 mg cohort), no DLTs occurred thus the RP2D of S was determined as 250mg qd. In the 16 evaluable pts, the best overall responses were 1 CR, 10 PRs and 5 SDs. The ORR was 68.8% and the DCR was 100%. 2 pts received R0 resection after 6 cycles' treatment. With a median follow up of 7.43 months, the estimated median PFS was 8.25 (95% CI: 4.57-NR) months and the 6-month PFS rate was 72.9%. Estimated median OS was 11.14 (95% CI: 5.52-NR) months and the 6-month OS rate was 82.5%. In the exploratory analysis, DDR-related mutations seemed predictive for better ORR (85.7% vs 55.6%, P= 0.308), PFS (6-month PFS rate:100% vs 53.3%, log-rank P= 0.519), and OS (6-month OS rate:100% vs 62.5%, log-rank P= 0.116). Treatment-related adverse events (TRAEs) occurred in 14 (77.8%) pts, and most common TRAEs (≥20%) included leucopenia (44.4%), hypertension (38.9%), and thrombocytopenia (22.2%). TRAEs of grade ≥3 included leucopenia, neutropenia, thrombocytopenia, and hypertension (n = 2 [11.1%] for each). There were no treatment-related deaths. **Conclusions:** These preliminary results showed encouraging anti-tumor efficacy and an acceptable safety profile of S plus K and GnP chemotherapy as 1L treatment for advanced PC. Clinical trial information: NCT05832892. Research Sponsor: HUTCHMED, ALPHAMAB.

Early treatment ctDNA dynamics to predict response to chemotherapy in patients with metastatic pancreatic cancer: A prospective, observational pilot study.

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Background: Assessment of chemotherapy response using imaging has limitations in metastatic pancreatic cancer whereas circulating tumor DNA (ctDNA) may offer an alternate assessment of tumor burden with improved lead-time. This study evaluated temporal ctDNA testing as a potential biomarker of treatment response data compared to standard-of-care CT scans in metastatic pancreatic cancer. **Methods:** In this prospective, observational, single-center trial, patients with metastatic pancreatic ductal adenocarcinoma starting a first-line (1L) or second-line (2L) systemic treatment regimen underwent imaging and frequent blood-based treatment assessment. CT imaging was obtained prior to and after 8 weeks of treatment, with response measured by RECIST 1.1 criteria. CA 19-9, CEA, and longitudinal ctDNA profiling using Signatera were performed at baseline, after 2 weeks, 4 weeks, and 8 weeks. A threshold of 20% decrease achieved or not was used to dichotomize ctDNA response and other cut-offs were evaluated in sensitivity analysis. Progression-free survival (PFS) was measured and compared to biomarker response. The primary objective was to evaluate the association of ctDNA changes at 4 and 8 weeks with PFS. Exploratory objectives included evaluation of response at 2-weeks, and comparison of PFS with CA 19-9 and CEA. **Results:** Between June and December 2023, 19 patients were enrolled. Sufficient tissue was available to perform tumor-informed ctDNA profiling in 12 of 19 patients (63%) undergoing systemic therapy with 7 patients (58%) starting on 1L therapy and 5 (42%) on 2L therapy. Overall median PFS was 4.0 months (4.2 months 1L, 3.3 months 2L). CtDNA response at 4-weeks was prognostic of PFS with a median decrease in ctDNA of 83.4% ($p = 0.0002$). CtDNA response at 8-weeks was also prognostic of PFS ($p = 0.01$). Three patients achieved ctDNA clearance of over 95% by week 4 and had a PFS of 5.9 months. Of, note there was one patient who had a 1-log decrease in ctDNA at 4-weeks, but a 20-fold increase at 8-weeks, whereas CEA and CA 19-9 were stable at 8-weeks, and this patient had subsequent disease progression 1 month later. In an exploratory analysis, ctDNA as soon as 2 weeks was also prognostic of recurrence ($p = 0.002$). In contrast to ctDNA, CA 19-9 and CEA did not show significance at any timepoint (2 weeks: $p = 0.2$ and $p = 0.8$, respectively; 4 weeks: $p = 0.7$ and $p = 0.8$, respectively; 8 weeks: $p = 0.8$ and $p = 0.5$, respectively). Sensitivity analysis showed that 20% decrease was robust; association at 4-weeks with ctDNA remained significant across a wide threshold range (-70% to +60%). **Conclusions:** Circulating tumor DNA predicts PFS as early as 2-weeks following treatment. These findings suggest clinical utility in measuring ctDNA in mPDAC as early as 2 weeks following treatment initiation within the context of prospective interventional clinical trials. Research Sponsor: Conquer Cancer, the ASCO Foundation.

TQB2868 combined with anlotinib and nab-paclitaxel plus gemcitabine as first-line treatment for metastatic pancreatic cancer: A prospective, multicenter, single-arm, phase 2 study.

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Background: Chemotherapy currently serves as the cornerstone for treating metastaticPancreatic Ductal Adenocarcinoma Cancer (mPDAC). Nevertheless, the survival of patients with mPDAC remains poor. Besides, the efficacy of single-agent immune checkpoint inhibitors or antiangiogenesis in the treatment of mPDAC is not satisfying. Therefore, it is important to explore combination therapy options for patients with mPDAC. TQB2868 injection is a bifunctional fusion protein that targets PD-1 and TGF-βRII. This trial was conducted to evaluate the effectiveness and safety of TQB2868 combined with anlotinib and nab-paclitaxel plus gemcitabine for mPDAC. **Methods:** This was a prospective, multicenter, single-arm phase II trial. Eligible pts were those who aged over 18 years, histologically or cytologically confirmed PDAC, have not received treatment before and radiographically showed distant metastases and measurable lesions. Patients received TQB2868 (300mg, I.V, D1,15) and Anlotinib (10mg, P.O, QD, D1-14), in addition to nab-paclitaxel (125mg/m^2, I.V,D1,8,15) and gemcitabine (1.0g/m^2, I.V, D1,8,15), administered over a 28-day treatment cycle.The primary endpoint was Progression-free Survival (PFS), Secondary end points included objective response rate (ORR) and disease control rate (DCR), overall survival (OS) and safety. The biomarker TGF-β1 was analyzed as exploratory results (NCT06767813). **Results:** 40 pts were enrolled and received TQB2868 combination regimen therapy, and the last follow-up time was January 10, 2025. 36 pts were eligible for response evaluation. With median follow-up duration of 5.9 months, the median PFS and OS have not been reached, with 6-month PFS and OS rates of 86% and 95%, respectively. The ORR was recorded at 63.9% (23/36) (95% CI, 46.2%-79.2%), with 23 pts achieving partial response. The DCR was 100% (36/36) (95% CI, 90.3%-100%). The most common TRAEs were neutropenia, thrombocytopenia, leukopenia, and anemia. Grade 3 TRAEs were reported in 52.5% pts (21/40). In exploratory analysis, the inhibition rate of TGFβ1 was over 90% in most cases after administration, with little to no rebound. **Conclusions:** TQB2868 combination regimen as first-line treatment was demonstrated to be tolerable, with promising anti-tumor activity in mPDAC. Clinical trial information: NCT06767813. Research Sponsor: None.

Phase II trial of serplulimab combined with gemcitabine plus nab-paclitaxel (GnP) and SBRT for metastatic pancreatic cancer as the first-line treatment.

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Background: The addition of anti-PD-1 monoclonal antibody (mAb) to gemcitabine and nab-paclitaxel (GnP) presented limited improvement in objective response rate (ORR) and disease control rate (DCR) for metastatic pancreatic ductal adenocarcinoma (mPDAC) in our previous study. Therefore, we conducted this phase II trial to evaluate the efficacy and safety of anti-PD-1 mAb (Serplulimab) plus GnP chemotherapy and stereotactic body radiotherapy (SBRT) in patients with mPDAC. **Methods:** Patients with mPDAC without previous treatment were enrolled to receive Serplulimab and GnP plus SBRT (SGSBRT) (intravenous infusion of Serplulimab 200 mg on day 1 every 3 weeks, gemcitabine 1000 mg/m^2 and nab-paclitaxel 125 mg/m^2 on day 1 and day 8, repeated every 3 weeks; SBRT delivered 5 fractions of 6.6 Gy to the primary tumor or 3 fractions of 8 Gy to the metastatic lesion in cycle 2) as the first-line treatment. The primary endpoint was 6-month progression-free survival (PFS) rate. Secondary endpoints included overall survival (OS), PFS, ORR, DCR, and adverse events (AEs). Moreover, the biomarkers such as circulating tumor DNA (ctDNA) and circulating hybrid cells (CHCs), PD-L1 expression, tumor tissue genetic status, cytokine levels, and immune microenvironment were also investigated. **Results:** As of January 2025, 47 patients have been enrolled and 41 patients have been followed for more than 6 months, with all 47 patients achieving efficacy according to the protocol. The 6-month PFS rate was 78.48%. The ORR was 74.47% (35/47), including 1 complete response (CR) and 34 partial responses (PR), and the DCR was 100%, with 12 stable disease (SD). The median PFS was 8.6 months, and the median OS was 15.5 months. The frequent grade 3 drug-related AEs were neutropenia (20/47, 42.55%), leukopenia (19/47, 40.43%), anorexia (18/47, 38.30%), and fatigue (11/34, 23.40%). The correlation between biomarkers and efficacy and prognosis are under-analyzed. **Conclusions:** This phase II study has met our preset primary endpoint with 78.48% in 6-month PFS rate, and SGSBRT presented promising efficacy with manageable safety profile and expected antitumor activity. This combination might be a promising option as first-line therapy for Chinese patients with mPDAC. Clinical trial information: ChiCTR2300073237. Research Sponsor: None.

First-line treatment with surufatinib, camrelizumab, nab-paclitaxel, and S-1 in locally advanced or metastatic pancreatic ductal adenocarcinoma (PDAC): A phase Ib/II randomized study.

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Background: PDAC is a highly aggressive cancer with limited treatment options. Previous reports of NCT05218889 showed promising efficacy of nab-Paclitaxel/S-1/Surufatinib/Camrelizumab (anti-PD-1 antibody) combination regimen (NASCA) in mPDAC (2023 ASCO abs# 4142; 2024 ASCO GI abs# 671). Here, we present the updated results. **Methods:** In phase Ib, a 3+3 dose escalation design was used to determine the RP2D of surufatinib. In phase II, patients were randomized 1:1 to receive the NASCA regimen or nab-paclitaxel plus gemcitabine (AG). The NASCA regimen was administered in 3-week cycles for up to 8 cycles. Patients without disease progression continued treatment with surufatinib, S-1, and camrelizumab, while the control group received AG regimen , q3w. Treatment continued until disease progression, unacceptable toxicity, withdrawal of consent, or death. The primary endpoints were DLTs and the RP2D of surufatinib in phase Ib, and the ORR in phase II. **Results:** As of Dec 16, 2024, 96 patients were enrolled in the study (6 in phase Ib, 90 in Phase II). In phase Ib, the RP2D for surufatinib was determined to be 200 mg (1 DLT out of 6 patients). In phase II, 45 patients were assigned to each group. Baseline characteristics were balanced between the groups. Most patients had metastatic disease (82.2% in NASCA vs 77.8% in AG). The NASCA group showed a confirmed ORR of 51.1% (23/45) versus 24.4% (11/45) in the AG group (OR: 3.2, 95% CI 1.3-8.2; p = 0.01). The median PFS were 7.9 and 5.4 months (HR: 0.63, 95% CI 0.40-0.99, p = 0.046), with 12-month OS rates of 55.5% (95% CI 39.4-68.9) in NASCA group and 52.7% (95% CI 36.6-66.5) in AG group. In the subgroup analysis of PFS, the NASCA group showed longer PFS in male patients (HR: 0.56, 95% CI 0.31-1.01), those with metastatic disease (HR: 0.57, 95% CI 0.35-0.94), and patients without liver metastasis (HR: 0.45, 95% CI 0.23-0.90). Furthermore, multiplex immunohistochemistry was performed on baseline tissue samples of 26 NASCA patients. The ratio of M1/M2 macrophage percentages was significantly higher in patients with PR than those with SD and PD (p = 0.04). Using the median as a cutoff, patients with higher levels of M1/M2 cells (p = 0.039), $CD8^+$ cells (p = 0.0024), and $CD8^+PD\text{-}1^+$ cells (p = 0.0064) in the stroma had longer PFS than those with lower levels. For Grade 3 and 4 TEAEs, the most frequently observed events in the NASCA group were decreased white blood cell count (31.1%), decreased neutrophil count (33.3%), and decreased lymphocyte count (20.0%). Similarly, these events were common in the AG group (26.7%, 28.9%, 8.9%, respectively). **Conclusions:** The NASCA regimen demonstrated promising efficacy with a manageable safety profile, showing a significantly higher ORR and longer PFS compared to AG group in patients with locally advanced or metastatic PDAC. Further studies are warranted to confirm these findings. Clinical trial information: NCT05218889. Research Sponsor: None.

First-line serplulimab and bevacizumab combined with nab-paclitaxel/gemcitabine followed by mFOLFOX in advanced pancreatic cancer: A phase II trial.

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Background: Patients with advanced pancreatic cancer (PC) have a poor prognosis, as this 'cold' tumor shows limited responsiveness to mono-immunotherapy. Chemotherapy may improve the efficacy of immunotherapy by reshaping the tumor immune microenvironment. We conducted a phase II trial to assess the anti-tumor activity and safety of first-line serplulimab (anti-PD-1) and HLX04 (a bevacizumab biosimilar) combined with nab-paclitaxel plus gemcitabine (nab-P/Gem), followed by modified FOLFOX (oxaliplatin, leucovorin, and 5-fluorouracil; mFOLFOX), in patients with locally advanced or metastatic PC. **Methods:** This single-arm phase II trial enrolled 37 patients with histologically or cytologically confirmed unresectable locally advanced or metastatic pancreatic ductal adenocarcinoma (NCT06393166). The study aims to increase the objective response rate (ORR) of the first-line sequential nab-P/Gem followed by mFOLFOX (nab-P/Gem-mFOLFOX) regimen from 50% to 68% with the addition of serplulimab and HLX04. The study employed Simon's minimax two-stage design, with a total of 23 patients achieving objective responses, thereby meeting the predefined primary endpoint. Secondary endpoints included progression-free survival (PFS), overall survival (OS), disease control rate (DCR), and safety. **Results:** Among the 37 patients analyzed, the average age was 62 years, and 22 patients (59.5%) were male. At baseline, patients had an adequate nutritional and performance status, with a mean BMI of 21.6 kg/m^2. Distant organ metastases were present in 34 patients (91.9%), with the liver being the most common site (n = 26, 70.3%). The confirmed ORR was 67.6% (95% CI, 49.5-82.6), including 1 patient with a complete response (CR), meeting the primary endpoint. Only 1 patient had progressive disease (PD) as the best response, yielding a DCR of 97.1% (95% CI, 84.7-99.9). As of the data cutoff in November 2024, the median follow-up was 6.1 months. The median PFS was 10.5 months (95% CI, 9.7-not reached), with a 6-month PFS rate of 80.0% (95% CI, 65.5-97.7). The median time to response (TTR) was 1.5 months, and the median duration of response (DOR) was 9.3 months. The OS remains immature. The incidence of treatment-related adverse events (TRAEs) was 83.8%, with grade ≥3 TRAEs occurring in 46.0% of patients. Hematologic toxicities were the most common treatment-emergent adverse events (TEAEs), and no fatal AE were observed. Overall, the treatment was manageable, and no new safety signals were identified. **Conclusions:** First-line serplulimab and HLX04 combined with nab-P/Gem-mFOLFOX demonstrates clinical feasibility and promising preliminary outcomes in advanced PC. Further follow-up is required to confirm the survival benefits, and following analyses are needed to explore the mechanisms underlying the efficacy of this novel regimen. Clinical trial information: NCT06393166. Research Sponsor: None.

AI-based predictive tool for detection of ctDNA in pancreatic adenocarcinoma using nationwide comprehensive genomic profiling data.

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Background: Comprehensive genomic profiling (CGP) has become a cornerstone of precision oncology, with liquid biopsy expanding its applicability. However, in some cases, circulating tumor DNA (ctDNA) is undetectable in liquid CGP, limiting the ability to assess genetic alterations. Identifying the optimal timing for liquid CGP remains a challenge. This study focuses on pancreatic adenocarcinoma, using nationwide CGP data and explainable AI methods to identify clinical factors associated with ctDNA detection. Based on these factors, we develop an easy-to-use AI tool to predict the probability of ctDNA detection in real-world settings. **Methods:** We conducted a retrospective analysis of nationwide CGP data collected from Jun 2019 to Dec 2023, covering 99.7% of CGP performed in Japan. Cohort 1 included 4,110 pancreatic adenocarcinoma cases analyzed by FoundationOne CDx, while Cohort 2 comprised 2,220 cases analyzed by FoundationOne Liquid CDx (F1L). Using clinical information available prior to CGP, we developed an eXtreme Gradient Boosting (XGBoost)-based predictive model to estimate ctDNA detection and employed SHapley Additive exPlanations (SHAP) analysis to elucidate contributing clinical factors. A smartphone application was deployed using the refined model. The app's performance was tested with Cohort 3, consisting of 629 pancreatic adenocarcinoma cases tested by F1L between Jan 2024 and Dec 2024. **Results:** In Cohort 1 (tissue), 98.5% of cases harbored mutations in either KRAS, TP53, CDKN2A, or SMAD4, confirming their role as surrogate markers for tumor-derived DNA detection. The predictive AI model for ctDNA detection, trained on Cohort 2 (liquid) data, achieved an AUROC of 0.754. SHAP analysis identified key predictors, including liver metastasis, the number of metastatic organs, performance status, response to recent therapy, interval from diagnosis to blood collection, and treatment line. Notably, patients with liver metastases exhibited a significantly higher rate of ctDNA detection ($p < 0.001$) compared to those without, whereas patients with peritoneal metastases demonstrated a lower rate of ctDNA detection ($p < 0.01$). A refined model incorporating representative predictors was deployed as a smartphone application. When tested on Cohort 3 (liquid), the application demonstrated predictive accuracy with an AUROC of 0.769 (sensitivity: 0.707, specificity: 0.769) and a Brier score of 0.194. **Conclusions:** This study identified clinical factors predictive of ctDNA detection in liquid CGP for pancreatic adenocarcinoma using explainable AI methods and nationwide CGP data. Based on these findings, a smartphone application was developed to predict the probability of ctDNA detection. By facilitating optimal timing of liquid CGP, this app has the potential to enhance patient access to effective therapies, contributing to improved clinical outcomes. Research Sponsor: None.

Using live true single-circulating tumor cell comprehensive genomics to show clonal evolution and tumor heterogeneity in pancreatic cancer management.

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Background: Traditional tissue and CtDNA biopsies have limitations in pancreatic ductal adenocarcinoma (PDAC) due to sampling bias and inability to capture tumor evolution effectively. ctDNA offers Tx decisions, longitudinal monitoring for recurrence, real-time tumor evolution, and responses. However, ctDNA success is limited by its low sensitivity often with NMDs. While single circulating tumor cell (sCTC) genomics may offer higher sensitivity, but challenged with selective capture of live sCTCs without leukocyte contamination. We address limitations by identifying both clonal and rare sub-clonal mutations in PDAC. We report CellBiopsy assay to capture and release of sCTCs, facilitated by ctDNA-integrated comprehensive genomic profiling (CGP) at a true single-cell. **Methods:** In an observational study, ten advanced PDAC patients receiving SOC were accrued with MCW IRB approved protocol (PREDICT-MCW NCT ID:NCT05802069). All patients gave consent to investigational interventions. Live sCTCs were isolated at baseline (BL) and follow-up (FL) using OncoIndx Ikon sCTC assay in 10 mL of blood. Live CTCs were captured using glass beads with anti EpCam antibody and released in 96 well plate assay. DNA from individually captured sCTCs was linearly amplified, followed by target enrichment using OncoIndx CGP assay. Sequencing libraries were prepared and sequenced on Illumina NextSeq2000 (500× depth). ctDNA underwent deeper sequencing at 10000x coverage. Data was processed using iCare software for sequence alignment and variant calling. **Results:** Prospectively, 74 live sCTCs were isolated at baseline and follow up (mean sCTC distribution 7). Post SOC treatment, 50% of the patients (5/10) exhibited a 30% reduction in sCTC count at FL. *NRAS* mutations were the most frequent alteration observed in sCTCs (40.5%), followed by *HRAS* (27%) and *TP53* (23%). Paired ctDNA predominantly revealed *KRAS G12* variants (40%). Additional divergent molecular alterations in sCTCs were accounted for in NRAS, TP53, SMAD4, and PIK3CA-MTOR-AKT pathways, providing insights into mechanisms of treatment resistance and disease aggressiveness. Samples with co-occurring *NRAS* and *TP53*, or *SMAD4*, mutations along with *ERBB2* amplification, were associated with aggressive disease. In FL sCTCs genomics revealed evolving molecular profiles enriched for activating variants in the PIK3CA-MTOR-AKT pathway compared to bulk tissue and ctDNA genomics at BL. **Conclusions:** Compared to ctDNA, sCTC CGP revealed heterogeneous molecular profile in PDAC, offering precise insights into tumor heterogeneity, clonal evolution, disease progression, and treatment outcome. Integrating paired DNA profiling of ctDNA and sCTC DNA may provide a more CGP landscape of PDAC. Ongoing analyses aim to evaluate temporal dynamics of CGP using ctDNA and sCTC DNA assay for advancing personalized management of PDAC. Clinical trial information: NCT05802069. Research Sponsor: None.

4165 Poster Session

Homologous recombination deficiency (HRD) profiling in Chinese pancreatic ductal adenocarcinoma: Implications for platinum-based chemotherapy.

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Background: Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive cancer with poor prognosis. While platinum-based therapies have demonstrated some therapeutic benefits, their associated toxicity underscores the need to identify patients who are most likely to respond. Homologous recombination deficiency (HRD) has been linked to improved sensitivity to platinum-based therapies, but its role in PDAC, particularly beyond *BRCA1* and *BRCA2* (*BRCA1/2*) mutations, remains poorly understood. **Methods:** A retrospective analysis was conducted on 264 Chinese patients diagnosed with PDAC. Genomic data were obtained using a targeted next-generation sequencing (NGS) panel, which included: (1) 28 canonical homologous recombination repair (HRR) genes (*BRCA1, BRCA2, PALB2, ATM, ATR, BAP1, BARD1, BRIP1, CDK12, CHEK1, CHEK2, EMSY, FAM175A, FANCA, FANCC, FANCD2, FANCL, FANCI, MRE11, NBN, PPP2R2A, PTEN, RAD50, RAD51B, RAD51C, RAD51D, RAD54B,* and *RAD54L*), along with their bi-allelic loss-of-function (BILOF) status; (2) 8 genes associated with other DNA damage repair (DDR) pathways (*TP53, CDH1, EPCAM, MLH1, MSH2, MSH6, PMS2,* and *STK11*); and (3) an integrated HRD score, calculated as the unweighted sum of loss of heterozygosity (LOH), telomeric allelic imbalance (TAI), and large-scale transitions (LST). HRD score $\geq$ 38 and/or *BRCA1/2* BILOF was predefined as HRD positive. The association between HRD status and clinical outcomes in patients treated with first-line platinum-based therapies was systematically analyzed. **Results:** Among the 264 PDAC patients, 6.4% (n = 17) were classified as HRD-positive, a larger group compared to the 1.9% (n = 5) with *BRCA1/2* BILOF. Overall, 19.3% (51/264) of patients harbored mutations in HRR genes. Among these, 4.9% (n = 13) had *BRCA1/2* mutations, with 38.5% (n = 5) exhibiting BILOF. The most frequently mutated HRR genes included *ATM* (4.2%) and *BRCA2* (3.8%), followed by *CHEK2* (1.5%), *BRCA1* (1.5%), *ATR* (1.5%), and *FANCA* (1.5%). The median HRD score was notably higher in patients with HRR gene BILOF (25.5) compared to those with non-BILOF (14). In the first-line platinum chemotherapy cohort (n = 133), HRD-positive patients exhibited significantly improved progression-free survival (PFS), with a median PFS of 20.5 months, compared to 11.3 months in HRD-negative patients (HR = 0.385, 95% CI: 0.177-0.84, P = 0.012). Notably, patients with *BRCA1/2* BILOF derived substantial clinical benefit from first-line platinum-based therapies, with no instances of disease progression or death during the treatment period. **Conclusions:** HRD profiling, defined by an HRD score threshold of $\geq$38 and/or *BRCA1/2* BILOF status, is a valuable biomarker for predicting response to platinum-based chemotherapy in PDAC. This study suggests that scar-based HRD marker and gene BILOF status could serve as predictive markers for PDAC personalized therapy. Clinical trial information: [2024]138. Research Sponsor: National Natural Science Foundation of China; 82330065, 30900650, 81372501, 81572260, 81172232, 31430030.

The differential effect of stromal genes on gemcitabine/nab-paclitaxel (GN) and GN/cisplatin (GCN) outcomes in advanced pancreatic adenocarcinoma (aPDAC).

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Background: GN is a front-line therapy for aPDAC. A Phase I/II study demonstrated that GCN has a higher overall response rate and median overall survival (mOS). Our previous study found no difference in outcomes among patients with DNA damage repair gene mutations; however, stromal gene expression correlated with mOS in patients receiving GCN. Here, we further evaluate differences in the outcomes with GCN and GN by site of biopsy. **Methods:** PDAC samples (n = 4,463) were analyzed by NGS (NextSeq/NovaSeq) or RNA (NovaSeq) (Caris Life Sciences, Phx, AZ). Expression of stromal and related genes (*ACTA2, ADIRF, HAS2, IL-6, MMP-2, MMP-9, SPARC, STAT3, TBGB1, TGFB2, TGFBR3, IDO1, HLA-DRB4, VEGFB)* from different biopsy sites [high expression (H) >50% of RNA transcripts per million] was correlated with outcomes to GCN or GN. mOS was obtained from insurance claims and calculated from first treatment to last contact. The hazard ratio (HR) was calculated by the Cox proportional hazards model, and p-values were calculated using the log-rank test. **Results:** 4325 patients [primary biopsy (PT), n = 1,878; non-liver metastatic biopsy (N-LM), n = 818; Liver biopsy (LM), n = 1,629] received GN while 138 patients (PT, n = 45; N-LM, n = 28; LM, n = 65) received GCN. GCN was associated with longer mOS than GN [Δ: 5.2 months (m), HR: 0.76, 95% CI 0.63-0.92, p = 0.01]. GCN was associated with longer mOS compared to GN in LM (Δ: 5.6 m, HR: 0.66, 95% CI 0.50-0.87, p = 0.003), but it was not significant in PT (Δ: 4.6 m, p = 0.13) and N-LM (Δ: 4.4 m, p = 0.35). Median *MMP2* (38.5 vs. 163.1 vs. 162.2), *VEGFB* (14.4 vs. 16.9 vs. 16.2) and *TGFBR3* (11.4 vs. 15 vs. 16.4) expression were lower in LM compared to PT and N-LM while *TGFB1* (41.6 vs. 34.5 vs. 39.8) and *IL6* (1.61 vs. 1.19 vs. 1.41) expression were highest in LM ($p < 0.05$). In LM, *IL6*-H (Δ: -11 m, p = 0.037) and *TGFB1*-H (Δ: -5.9 m, p = 0.10) were associated with worse post-GCN survival compared to GN (p = 0.82 and p = 0.57). Whereas, in N-LM, *TGFBR3*-H trended towards longer post-GCN survival (Δ: 12 m, p = 0.18), while *ADIRF*-H trended towards shorter post-GCN survival (Δ: -12 m, p = 0.056) compared to GN (p = 0.42 and p = 0.10). While in PT, *MMP2*-H (Δ: 11.3m, HR: 0.46, p = 0.16), *TGFB1*-H (Δ: 11.3 m, HR: 0.33, p = 0.09), *HLA-DRB4*-H (Δ: 12.9 m, HR: 0.44, p = 0.11) and *VEGFB*-H (Δ: 10.7, HR: 0.34, p = 0.09) trended towards longer post-GCN survival compared to GN (*MMP2*-H, Δ: 3.4 m, p = 0.03, *TGFB1*-H, p = 0.661, *HLA-DRB4*-H, p = 0.67, *VEGFB-H*, Δ: 1.3 m, p = 0.03). **Conclusions:** GCN is associated with improved mOS compared to GN, especially in LM.Stromal gene expression in the liver differs from that in N-LM and the pancreas. While high stromal gene expression trends towards worse post-GCN survival in LM, it is associated with improved survival in N-LM and PT. Further validation is needed to understand the impact of stromal gene expression in different tumor sites on survival outcomes and signature development. Research Sponsor: None.

CheMo4METPANC: Combination chemotherapy (gemcitabine and nab-paclitaxel), chemokine (C-X-C) motif receptor 4 inhibitor (motixafortide), and immune checkpoint blockade (cemiplimab) in metastatic treatment-naïve pancreatic adenocarcinoma—Updated clinical and translational findings.

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Background: Metastatic pancreatic ductal adenocarcinoma (mPDAC) is a uniformly fatal disease with an immunosuppressive tumor microenvironment (TME). In our KPC mouse model study, targeting the C-X-C motif chemokine receptor 4 (CXCR4)/C-X-C motif chemokine ligand 12 (CXCL12) axis in combination with αPD-1, and gemcitabine improved survival when compared to mice treated with gemcitabine or other combinations. The goal of this first-in-human study was to evaluate safety, radiologic response rate, and change in tumor microenvironment (TME) elicited by motixafortide (CXCR4i), cemiplimab (αPD1), gemcitabine, and nab-paclitaxel (MCGN) in treatment-naïve mPDAC. **Methods:** CheMo4METPANC is an open label, multicenter, investigator-initiated, study evaluating MCGN in mPDAC (NCT04543071). Here we report the updated results of the signal seeking phase of this study. The primary aim was to study the safety of MCGN. All patients received pre- on-treatment and optional on-progression biopsies. Single nucleus RNA sequencing (snRNAseq) and quantitative multiplex immunofluorescence (qmIF) were used to characterize the TME. **Results:** A total of 11 patients (1 over-enrolled) participated in the study at Columbia and Brown Universities (11/9/2020-3/3/2023). The median age was 58 years. As of 04/22/24 (median follow up 23 months), 7 (63%) and 3 (27%) patients experienced a partial response (PR) and stable disease, respectively. One patient experienced radiologic resolution of hepatic metastasis and underwent definitive radiation therapy to the primary tumor. A second had a sustained PR (11 months) and underwent pancreaticoduodenectomy and hepatic wedge resection which revealed a pathologic complete response within the hepatic and primary lesion. Median progression free survival (PFS) was 9.6 months. The most common adverse events experienced while on the study combination included skin hyperpigmentation (11/11), alopecia (10/11) and injection site reaction (9/11). The most common grade 3 or greater adverse events were anemia (5/11) and rash (3/11). Analysis of the TME revealed an increase in intratumoral CD8+ T-cells in all patients, and that patients achieving a PR were found to have higher proportions pre-treatment of CXCL12-producing cancer associated fibroblasts, a potential marker of response. **Conclusions:** Preliminary results from this pilot study of MCGN in mPDAC were promising, with a PR rate of 63% and disease control rate (DCR) of 91%. Based on these results, the study was amended to transition to a randomized phase 2 trial testing MCGN compared to GN (2:1; N = 108). The primary endpoint is PFS. The phase 2 study is actively enrolling patients and incorporates optional paired research tumor biopsies. Clinical trial information: NCT04543071. Research Sponsor: BioLine Rx and Regeneron Pharmaceuticals.

Phase 1/2 study of nivolumab and ipilimumab combined with gemcitabine, nab-paclitaxel, and adaptive stereotactic body radiotherapy in bordeline resectable, locally advanced or metastatic pancreatic cancer (LAPTOP).

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Background: This phase 1/2 study (NCT04247165) evaluated the safety and efficacy of combining nivolumab, ipilimumab, gemcitabine, nab-paclitaxel, and adaptive stereotactic body radiotherapy (SBRT) in patients with borderline resectable (BRPC), locally advanced (LAPC), or metastatic pancreatic cancer (mPC). **Methods:** Treatment-naïve patients with BRPC, LAPC or mPC received 28-day cycles of nivolumab (3 mg/kg), ipilimumab (1 mg/kg single dose), and gemcitabine (800 mg/m^2) with nab-paclitaxel (100 mg/m^2 on days 1, 8, and 15). Starting in cycle 3, patients underwent MRI or CT-guided adaptive SBRT (8 Gy x 3 fractions) targeting the primary pancreatic tumor. Primary endpoint: safety, defined by the incidence of treatment-related adverse events (TRAEs) leading to discontinuation, monitored via a Bayesian stopping rule for rates exceeding 30%. Secondary endpoints: OS, PFS, ORR, DCR, DOR, and resection rate. Exploratory endpoint: immunological changes. **Results:** A total of 55 patients received at least one treatment (BRPC: n=1, LAPC: n=23, mPC: n=31), with a median follow-up of 27.6 months (IQR 26.3-34.4) calculated via reverse Kaplan-Meier. Grade 3-4 TRAEs occurred in 70.8% of BRPC/LAPC and 71.0% of mPC patients. No grade 5 TRAEs were observed. Treatment discontinuation due to TRAEs occurred in 20.8% (BRPC/LAPC) and 9.7% (mPC). Median OS: 23.0 months (95% CI: 11.4–NR) for BRPC/LAPC and 11.2 months (6.8–15.8) for mPC. Median PFS: 14.9 months (8.7–24.2) for BRPC/LAPC and 6.1 months (3.8–8.4) for mPC. ORR: 33.3% (15.6–55.3) for BRPC/LAPC and 19.4% (7.5–37.4) for mPC. DCR: 75.0% (53.3–90.2) for BRPC/LAPC and 61.3% (42.2–78.2) for mPC. Median DOR: 8.9 months (4.0–12.7). Nine (37.5%) BRPC/LAPC patients and three (9.7%) mPC patients underwent resection. Preliminary analyses revealed treatment-induced T-cell activation, particularly after SBRT, with upregulation of activation and stemness markers in patients with durable clinical benefit. Conversely, an increase in senescence markers was observed in the rest of the cohort. **Conclusions:** The combination of nivolumab, ipilimumab, gemcitabine, nab-paclitaxel, and adaptive SBRT demonstrated an acceptable safety profile and efficacy supporting further investigation in BRPC, LAPC, and mPC patients. Clinical trial information: NCT04247165. Research Sponsor: None.

Clinico-genomic characterization of *PALB2*-mutated pancreatic adenocarcinoma.

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Background: Pancreatic adenocarcinoma (PDAC) with germline (g) or somatic (s) mutations in *BRCA1/2* and *PALB2* exhibit unique molecular characteristics and predict response to platinum-based chemotherapy and PARP inhibition. However, distinct features of *PALB2* and PDAC are not well described. Herein, we characterize distinct clinico-genomic features of patients (pts) with g/s *PALB2* and PDAC. **Methods:** Institutional databases and cBioPortal were queried to identify pts with g/s*PALB2* and PDAC. Pts with *PALB2* variants of unknown significance (VUS) were excluded (annotation from OncoKb, ClinVar). Demographic data and clinical outcomes abstracted from medical record. Detailed mutational analysis obtained from cBioPortal. Zygosity determined with FACETS. Progression-free survival (PFS) and overall survival (OS) estimated with Kaplan-Meier Method. **Results:** N = 29 pts with pathogenic/oncogenic g/s*PALB2* and PDAC identified between 2011-2024. N = 25 (86%) g*PALB2* (+/- s*PALB2*) and N = 4 (14%) s*PALB2* (no g*PALB2*); N = 13 s*PALB2* excluded as VUS. Median age (range): 57 years (38-78) g*PALB2* and 63 years (43-73) s*PALB2*. N = 23 (79%) white; N = 16 (55%) female. Stage IV at diagnosis: N = 11 (44%) g*PALB2*; N = 2 (50%) s*PALB2* cohort. In g*PALB2* cohort (N = 25), 4 (16%) had personal history of cancer (N = 2 thyroid, N = 1 uterine, N = 1 CLL) and N = 17 (68%) had family history of cancer (N = 7 breast/prostate/ovarian, N = 1 pancreas). *KRAS* and *TP53* variants co-occurred in 84% and 36% of g*PALB2* and 50% and 50% of s*PALB2* cases, respectively. N = 9 (56%) of patients with a *gPALB2* mutations showed biallelic loss of *PALB2* (N = 6 by LOH, N = 3 somatic LOH). None of four patients in s*PALB2* cohort (negative g*PALB2*) had biallelic loss. Median TMB (mt/Mb): 4.10 (0.80-9.10) g*PALB2*; 3.85 (2.00-5.80) s*PALB2*. For stage IV g*PALB2* (N = 11), median PFS 4.2 months (95% CI 2.4, NR) and median OS 12 months (95% CI 5.5, NR). N = 10 (90%) received platinum therapy, with N = 6 in the first line setting. Durable disease control on PARPi was observed for patients with g*PALB2* and s*PALB2*, including N = 1 s*PALB2* with 7 months on 4th-line olaparib and N = 1 g*PALB2* with 6 months on 6th line Olaparib. **Conclusions:** *gPALB2* and *sPALB2* mutations are seen in a small % of PDAC. *gPALB2* PDAC presents earlier and is linked to family history of cancer. g*PALB2* compared to s*PALB2* had higher biallelic loss; oncogenic s*PALB2* are uncommon. Identification of g/s*PALB2* has implication for therapeutics and screening. Loss of heterozygosity, TMB, telomeric allelic imbalance, large-scale state transitions, and implications for treatment will be presented. Research Sponsor: None.

	***gPALB2* = 25**
Putative driver mut (%)	21 (84)
Truncating mut	13 (62)
Structural Variant	4 (19)
Splice mut	4 (19)
Zygosity	
Biallelic	9 (56)
Monoallelic	6 (44)
Unknown	10

Prognostic and predictive impact of next-generation sequencing in metastatic pancreatic ductal adenocarcinoma.

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Background: Outcomes in *de novo* metastatic pancreatic ductal adenocarcinoma (mPDAC) remain dismal, although considerable heterogeneity exists in responses to therapy and survival. With increased use of tumor-cell next-generation sequencing (NGS) in mPDAC, improved understanding of the prognostic and predictive value of genomic alterations is needed. **Methods:** Between 2019-2023, 949 PDAC patients (pts) underwent targeted NGS (Oncomine), of which 161 had *de novo* metastatic disease. Progression-free survival (PFS) after front-line therapy and overall survival (OS) were correlated with clinical parameters and genomic alterations. Long-term survival (LTS) was defined as OS in the top quartile. **Results:** In pts who underwent at least one dose of systemic therapy (80%, n=128), mPFS and mOS were 6.6 and 10.4 months. Pts who received 5-FU-based front-line therapy (97% received a triplet with oxaliplatin and irinotecan or liposomal irinotecan) had improved outcomes compared to pts who underwent gemcitabine-based therapy (89% gemcitabine/nab-paclitaxel [gem/nab-P]; mOS 13.2 vs 7.3 months, HR 0.66, 95% CI 0.45-0.97). Tumor mutational burden (TMB), pathogenic mutations in genes involved in cell-cycle regulation (CCR) and DNA damage response (DDR), and loss of *SMAD4* were not associated with broad differences in PFS/OS. As expected, in pts treated with 5-FU/platinum, mutations in DDR genes were associated with LTS (p = 0.04). *KRAS* mutational status was prognostic (Table; p = 0.02 for OS). Surprisingly, *KRAS* wild type (WT) pts had poorer PFS/OS compared to *KRAS*-mutated pts. However, 3/12 *KRAS* WT pts, all with Class II *BRAF* and *TP53* loss-of-function (LOF) mutations, were unable to tolerate any systemic therapy. In 3 *KRAS* WT pts with LTS, 2 had mutations in DDR genes and TMB > 10 Mut/Mb, while 2 had mutations in CCR genes. Multivariate analysis confirmed improved LTS of pts harboring *KRAS G12R* compared to *G12D* (OR 0.22, 95% CI 0.07-0.72, p = 0.01). *TP53* was mutated in 75% of pts (18% gain-of-function [GOF]). WT *TP53* was associated with improved survival (mOS 10.7 vs 5.0 months, HR 0.60, 95% CI 0.43-0.84). Interestingly, in pts receiving gem +/- nab-P, LTS was lacking in those with *TP53* GOF mutations but not LOF mutations (p = 0.13), a trend not seen in pts receiving 5-FU/platinum. **Conclusions:** Herein we show novel prognostic and predictive significance of genomic alterations in mPDAC. Heterogeneity exists in *KRAS* WT pts with *BRAF* and *TP53* mutations conferring poorer prognosis and DDR and CCR gene mutations associated with LTS. *KRAS G12D* is associated with worse outcomes compared to *G12R* while *G12V* is intermediate. Pts with *TP53* GOF mutations may benefit from 5-FU/platinum upfront. Research Sponsor: None.

***KRAS* mutational status, frequency, and survival.**

KRAS Status	N	%	mPFS (months)	mOS (months)
WT	12	7.5	3.1	3.5
G12C	2	1.2	2.1	2.1
G12D	70	43.5	5.0	6.6
G12R	25	15.5	9.7	13.2
G12V	36	22.4	4.9	10.5
Q61H/R	14	8.7	4.3	5.6
Other	2	1.2	5.5	7.8

Interpretable artificial intelligence-driven selection of doublet chemotherapy regimens as second-line treatment in patients with advanced pancreatic cancer.

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Background: Guidelines recommend second-line (2L) doublet chemotherapy, NALIRI (liposomal irinotecan + 5-fluoruracil and leucovorin), FOLFIRI or FOLFOX, for patients (pts) with metastatic pancreatic ductal adenocarcinoma (mPDAC) after failure of gemcitabine+Nab-paclitaxel (GemNabP). A head-to-head comparison between doublets has not been performed. We aimed to apply interpretable artificial intelligence (IAI, i.e., AI systems in which the prescription logic can be understood) methods on real-world data to establish which pts should receive NALIRI *vs* other doublets to maximize the benefit in this setting. **Methods:** In this observational cohort study, we compared progression-free survival (PFS) of consecutive pts with mPDAC who received 2L doublets after GemNabP failure at 42 Italian centers between 2013 and 2023. The dataset was randomly split into a training set (70%) and a test set (30%). In the former, a counterfactual Cox proportional hazard model, including baseline characteristics to infer the 12-month PFS probability for a given patient under each regimen, was trained. An Optimal Policy Tree (OPT), a state-of-the-art IAI-based method, was used to read the complete reward matrix by training a decision tree with the counterfactual predictions, and OPT recommendations were validated in the test set. The potential gain of the new policy was evaluated by 12-month PFS net-benefit curves. **Results:** Among 571 eligible pts, 209 (36.6%), 209 (36.6%) and 153 (26.8%) received NALIRI, FOLFOX and FOLFIRI, respectively. Median PFS was similar among the three groups (3.3 months for NALIRI, 3.5 months for FOLFOX and 3.6 months for FOLFIRI), with a long-term benefit observed only in the NALIRI group (12-month PFS 12.0% *vs* 2.6% for FOLFIRI and 5.2% for FOLFOX). The OPT recommended NALIRI as the preferred regimen for pts with pancreatic head/body cancers, with ECOG PS 0 or with Ca19.9 $<$ 109 U/ml if ECOG PS $>$ 0. The net-benefit curves revealed that the OPT consistently outperformed the uniform strategies of administering either NALIRI or FOLFOX/FOLFIRI to all pts, attaining a 2.5 percentage-point net-benefit at a threshold probability of roughly 9%. **Conclusions:** Our findings show that 2L NALIRI can offer long-term PFS advantage in a subgroup of mPDAC pts compared with other doublets. The AI-derived policy provides a higher net benefit than treating all pts with NALIRI, avoiding unnecessary clinical and financial toxicity. Research Sponsor: None.

First safety analysis of an open-label, single arm phase II trial investigating the efficacy, safety and quality of life of neoadjuvant chemotherapy with liposomal irinotecan combined with oxaliplatin and 5-fluoruracil/folinic acid followed by curative surgical resection in patients with hepatic oligometastatic adenocarcinoma of the pancreas (HOLIPANC).

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Background: Aim of the prospective single arm HOLIPANC trial (NCT04617457) is to evaluate the efficacy and safety of multimodal treatment in pancreatic oligometastatic disease. **Methods:** Patients with hepatic oligometastatic pancreatic cancer receive up to 8 cycles of a combination of liposomal irinotecan (nal-IRI, 50mg/m^2) with 5-fluouracil (5-FU 2400mg/m^2)/folinic acid (FA, 400mg/m^2) and oxaliplatin (OX, 60mg/m^2) (Nal-IRIFOX) as neoadjuvant therapy followed by curative intended surgical resection of the primary tumor and liver metastases. Here, we present the first preplanned safety analysis with patients (pts) that were enrolled between 10/2021 and 04/2024. **Results:** A total of 56 pts were included in the analysis, of which 43 (77%) pts received at least 4 cycles and 16 (29%) pts 8 cycles of chemotherapy. Dose reductions of nal-IRI were required in 24 (43%) pts. Treatment-emergent adverse events (TEAE) were observed in 52 (93%) pts, 40 (72%) TEAEs were related to the neoadjuvant chemotherapy. Grade 3-4 TEAEs occurred in 30 (54%) pts, most common were gastrointestinal disorders, i.e. diarrhoea (n = 5), vomiting (n = 4) and nausea (n = 4). Hepatobiliary disorders (cholangitis (n = 5), cholestasis (n = 4)) and increased gamma-glutamyltransferase (n = 4) were also frequent but generally not considered in relation to the chemotherapy. Grade 3 anemia and leukopenia were observed in 3 (5%) and 2 (4%) pts respectively. Serious TEAEs occurred in 23 patients (41%). Next to the above mentioned gastrointestinal and hepatobiliary disorders, dehydration (n = 3) and infections (n = 2) were the remaining recurring events. At the time of analysis, resection was performed in 20 pts (36%). Overall postoperative complications occurred in 7 pts (35%), n = 2 (10%) were classified as Dindo-Clavien grade $\geq$ 3. Clinically relevant pancreatic fistula was shown in 1 patient (5%). While there were no deaths related to chemotherapy or surgery, 2 pts died because of tumor progression during follow-up within 28 days of chemotherapy administration or surgery. **Conclusions:** This analysis shows for the first time safety data from a prospective clinical trial of multimodal treatment in oligometastatic pancreatic cancer. As we show, the concept of neoadjuvant chemotherapy followed by surgery is safe, the toxicity and overall morbidity is not elevated compared to available data from the NAPOLI-3 trial, even in combination with a following tumor resection after neoadjuvant treatment. Clinical trial information: NCT04617457. Research Sponsor: None.

Circulated T-cell exhausted subtypes to predict response in PDAC patients.

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Background: In-depth analysis of T-cell exhausted subsets in the circulation of Pancreatic Ductal Adenocarcinoma (PDAC) patients may provide insights into novel therapeutic options and predictive biomarkers. We performed a detailed immunophenotypic analysis for both early-stage (resectable) and metastatic (unresectable) PDAC patients. Additionally, different T-cell populations were correlated with clinical outcome. **Methods:** Fifty-five treatment naive PDAC patients, twenty-five of which had resectable disease, and ten healthy donors (HD) were enrolled. Peripheral Blood Mononuclear Cells (PBMCs) were isolated and stained with fluorochrome-conjugated monoclonal antibodies. Multicolor flow cytometry was performed to determine differences between T-cell populations and their correlation with clinical outcome. **Results:** Advanced disease patients that harbored high percentages of $CD4^+PD\text{-}1^+$ T_{eff} cells had longer PFS (median: 190 vs. 100 days, p:0.030) and OS (median: 250 vs. 170 days, p: 0.041) while for early-stage patients high percentages of $CD8^+PD\text{-}1^+T_{eff}$ displayed longer DFS (median: 422 vs. 200 days, p:0.044) and OS (median: Und vs. Und days, p:0.041). For early-stage patients, high percentages of both $CD4^+$ and $CD8^+$ T-cells expressing $PD\text{-}1^+TCF1^+$ (exhausted cells) were predictive for survival ($CD3^+CD4^+PD\text{-}1^+TCF1^+$: med. Und vs. 277 days, p:0.0041) and ($CD3^+CD8^+PD\text{-}1^+TCF1^+$: med. Und vs. 390 days, p:0.042). Additionally, expression levels of PD-1 (MFI levels) were substantially elevated in the $PD\text{-}1^+TCF1^-$ subset for both early stage $CD3^+CD4^+$ (p:0.026), $CD3^+CD8^+$ (p: = 0.006) and advanced-stage, (p:0.0001 and p:0.045, respectively), implying that terminally exhausted ($PD\text{-}1^+TCF1^-$) T-cells exhibit higher PD-1 expression than primarily exhausted ($PD\text{-}1^+TCF1^+$). For advanced stage patients, high levels of $CD57^+$, a marker of terminally differentiated T-cells, in $CD3^+CD8^+$ were associated with improved PFS (118 vs. 92 days, p:0.178)and OS(271 vs. 152 days, p: 0.019), $CD3^+CD8^+PD\text{-}1^+TCF1^+$ (PFS: med. 260 vs. 60 days, p = 0.0063 ; OS: 271 vs. 90 days, p: 0.003) and $CD3^+CD8^+PD\text{-}1^+TCF1^-$ T-cells (PFS: med. 188 vs. 80 days, p = 0.0459 ; OS: 271 vs. 107 days, p = 0.0429). $CD57^+$ T-cells were not correlated with response in early-stage patients. **Conclusions:** T-cell exhaustion represents ineffective immune response and in both early and advanced-stage PDAC may predict clinical outcome offering opportunities for innovative therapeutic options for this fatal disease. Research Sponsor: None.

USP22 as promoter of Treg cell infiltration and modulator of immunotherapy efficacy through the PIAS1/P65/CCL22 pathway in pancreatic cancer.

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Background: Immune checkpoint inhibitors targeting PD-1 and CTLA-4 have shown success in various cancers; however, their efficacy in pancreatic cancer remains limited, likely due to its immunosuppressive microenvironment. Treg cells are crucial in tumor immune evasion and suppression. Targeting Treg cells is an emerging strategy in pancreatic cancer immunotherapy. Recent studies show that USP22 (Ubiquitin-Specific Protease 22) regulates immunity by deubiquitinating key proteins like PD-L1 and STAT1 in tumor cells, while in Treg cells, USP22 controls FoxP3, modulating Treg cell function. This study aims to explore how USP22 regulates the immune microenvironment in pancreatic cancer and identify potential targets to enhance immune checkpoint blockade responses. **Methods:** Bioinformatics analysis of tissue microarrays and the TCGA database was used to assess the correlation between USP22 and Treg cell infiltration in pancreatic cancer. 2. Tumorigenicity assays, immunohistochemistry, and flow cytometry were performed in C57BL/6 mice to determine the effect of USP22 on Treg cell infiltration. 3. Transcriptomic and proteomic analyses were conducted to explore the mechanisms by which USP22 regulates Treg cell infiltration. 4. In vitro experiments, including Western blot, qRT-PCR, immunofluorescence, deubiquitination assays, and chromatin immunoprecipitation, were used to identify the specific mechanisms of USP22 in regulating Treg cell infiltration. 5. The combination of PD-1 monoclonal antibody and nab-paclitaxel chemotherapy was tested to determine if targeting USP22 improves immunotherapy efficacy. **Results:** Immunohistochemistry and bioinformatics analysis revealed a significant positive correlation between USP22 expression and Treg cell infiltration in pancreatic cancer. 2. Tumorigenicity assays in C57BL/6 mice showed that USP22 promotes tumor growth and Treg cell infiltration. 3. Transcriptomic analysis found a strong association between USP22 and the TRAF1/NF-κB signaling pathway as well as CCL22 expression. 4. In vivo and in vitro experiments confirmed that USP22 activates TRAF1/NF-κB signaling and increases CCL22 release, promoting Treg cell infiltration. 5. USP22 deubiquitinates PIAS1, inhibiting its nuclear translocation and activating p65. 6. USP22 knockdown improved therapeutic responses to combined immunotherapy (PD-1 inhibitors) and chemotherapy (nab-paclitaxel). **Conclusions:** USP22 promotes Treg cell infiltration in pancreatic cancer by deubiquitinating PIAS1, inhibiting its nuclear translocation, and activating the TRAF1/NF-κB signaling pathway, which leads to CCL22 release. Targeting USP22 could inhibit cell proliferation, promote apoptosis, and remodel the immune microenvironment, enhancing the efficacy of immune checkpoint blockade therapy. Research Sponsor: None.

LBA4175 **Poster Session**

NAPOLI 3, a phase 3 study of NALIRIFOX in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC): Final overall survival (OS) analysis and characteristics of the long-term survivors.

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Biomarkers of response to immunotherapy in pancreatic ductal adenocarcinoma (PDAC) with homologous recombination deficiency (HRD).

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Background: PDAC is associated with a paucity of immune effector cells, low antigenicity, and immunosuppressive factors in the tumor microenvironment (TME); consequently, treatment of unselected PDAC patients with immune checkpoint inhibitors (ICIs) has been ineffective. In HRD-PDAC, dual PD-1/CTLA-4 ICI therapy has a response rate of 14-42%. In this study, we investigated biomarkers of immunotherapy response in PDAC tumors with HRD. **Methods:** We generated a murine model of HRD-PDAC and performed transcriptomic analysis of mouse responders versus non-responders to ICI therapy to identify biomarkers of response. DNA and RNA sequencing was also performed for patient tumor samples submitted to Caris Life Sciences. Samples harboring pathogenic or likely pathogenic (P/LP) *BRCA1*, *BRCA2* or *PALB2* mutations were classified HRD, the remaining samples non-HRD. Microsatellite instability-high neoplasms were excluded. TMB-High (TMB-H) was defined as ≥10 mutations/Mb. PD-L1 positivity was determined by IHC (SP142, ≥2+, ≥5%). High genomic loss of heterozygosity (gLOH-H) was defined as LOH at ≥16% of segments analyzed (up to 552). Immune cell infiltration was estimated by RNA deconvolution using quanTIseq. Mann-Whitney U, Fisher's Exact, or Chi-squared tests were used to determine statistical significance (p), with multiple comparisons corrections as appropriate (q). **Results:** In murine HRD-PDAC tumors, chronic platinum exposure was a biomarker for response to ICI. Responding tumors had differential enrichment of cytosolic DNA sensing and cGAS-STING-related pathways, and secretomes significantly enriched for the T-cell attractant chemokines CXCL9 and CXCL10. Of 6396 human PDAC samples, 4.2% were HRD (2.7% *BRCA2*, 0.9% *BRCA1*, 0.6% *PALB2* P/LP), and 95.8% non-HRD. Compared to the non-HRD cohort, the HRD cohort was younger (median age: 66 vs 68 years, p = 0.0006), had lower prevalence of *TP53* (57.4% vs 79.0%, q < 0.0001), *CDKN2A* (14.1% vs 24.7%, q = 0.0062), and *RNF43* (0.8% vs 5.8%, q = 0.0322) mutations, and was more frequently PD-L1+ (21.7% vs 14.0%, q = 0.0460), TMB-H (6.4% vs 1.9%, q = 0.0001), and gLOH-H (41.2% vs 9.5%, q < 0.0001). Median infiltration of M1 macrophages was higher in the HRD cohort (6.2% vs 5.3%, p = 0.0028), while that of M2 macrophages was lower (2.9% vs 3.3%, p = 0.0081).TheHRD cohort demonstrated higher median expression measured in transcripts per million of *CGAS* (6.3 vs 5.4 TPM, p = 0.0002), *CXCL9* (2.19 vs 1.60 TPM, p = 0.0015), and *CXCL10* (4.65 vs 3.65 TPM, p = 0.0308), phenocopying observations in the murine model. **Conclusions:** PDAC tumors associated with canonical HRD variants (*BRCA1/2*, *PALB2*) have distinct genomic, transcriptomic, and TME features which are immune-permissive and explain the sensitivity of this subgroup of patients to ICI therapy. Understanding the underlying mechanisms could inform strategies to broaden the impact of ICI in this population. Research Sponsor: None.

Interim open-label phase 1 results of misetionamide (GP-2250): A small molecule antineoplastic targeting three major transcription factors.

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Background: GP-2250 is a novel antineoplastic agent demonstrating effective activity on preclinical pancreatic cancer models alone or in combination with gemcitabine, and inhibits c-MYC, NFκB, and HIFα in cancer cells at clinically achievable concentrations. This open-label phase 1 trial (NCT03854110) evaluates the safety and tolerability of escalating doses of GP-2250 in combination with gemcitabine as a second-line treatment in adults with advanced pancreatic adenocarcinoma that experienced disease progression with 5-FU based chemotherapy. **Methods:** GP-2250 dose escalation (starting dose 250 mg escalating up to 40 g IV once weekly) followed a Bayesian Optimal Interval design which transitioned to a 3+3 design. A 1-week run-in of GP-2250 was followed by a full cycle (3 weeks on, 1 week off) of GP-2250 plus gemcitabine treatment for each of 11 dose cohorts. Single-patient cohorts with 100% escalation between cohorts were enrolled until the first DLT (or cohort 4), followed by 3 patient cohorts with 35%−45% escalation between cohorts. The DLT assessment period was 5 weeks at each dose. Patients were treated until disease progression or development of unacceptable toxicity. Primary endpoints were safety and tolerability of GP-2250 monotherapy and in combination with gemcitabine. Secondary and exploratory endpoints were preliminary efficacy, pharmacokinetics, and pharmacodynamic blood markers. **Results:** To date, 52 patients have been enrolled. Five serious adverse events were reported in 3 patients (2 CVAs, pneumonia, and abdominal and flank pain in 2 patients), none attributed to GP-2250. Three patients discontinued treatment: 1 disease hyperprogression (at 11 g GP-2250) and 2 neutropenia (at 21 g GP-2250), with only 1 event of grade 3 neutropenia "possibly" attributed to GP-2250. In summary, the addition of GP-2250 did not significantly alter the safety and tolerability expected of gemcitabine alone. Twelve patients (23%) had progression-free survival (PFS) of ≥16 weeks, or twice as long as historical gemcitabine treatment alone; 7 patients (13%) had PFS of 24 weeks, and 4 (8%) had PFS of 32 weeks. One patient survived > 2 years while receiving treatment. Seventeen patients (33%) achieved stable disease and 6 (12%) achieved a partial response by RECIST criteria. While the blood half-life of GP-2250 is ~5 hours, mTOR and AKT biomarker data indicate that the biological half-life is longer, at 4–5 days. These data are within the concentrations and times required for cytotoxicity in all cancer cell lines tested with GP-2250. **Conclusions:** GP-2250/gemcitabine combination therapy showed encouraging safety and tolerability and favorable PFS outcomes compared to gemcitabine alone. These promising results in a historically difficult to treat pancreatic cancer population warrant progress to later-stage studies. This study is funded by Geistlich Pharma AG. Clinical trial information: NCT03854110. Research Sponsor: Geistlich Pharma AG.

Concurrent mutations in DNA damage repair genes *BRCA1*, *POLE*, *ATM* and *FANCA* to predict overall and progression-free survival for patients (pts) with metastatic pancreatic ductal adenocarcinoma (mPDAC) treated with chemotherapy in combination with dual checkpoint inhibition in the CCTG randomized PA.7 trial.

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Background: CCTG PA.7 (NCT02879318) was a randomized phase II trial comparing gemcitabine (G) and nab-paclitaxel (N) with and without dual immune checkpoint inhibition with durvalumab (D) and tremelimumab (T) as 1st-line therapy in pts with mPDAC. Matched plasma and tissue-based sequencing was performed for exploratory correlative biomarker analysis. **Methods:** Pts received G+N+D+T (n = 11 run-in, 119 randomized, 2:1 randomization) or G+N (n = 61). Long-term trial analysis was performed with a median follow-up time of 81.6 months. Correlative analysis was performed for pts with baseline ctDNA sequencing using a 600-gene PredicineATLAS panel (n = 173), with a subset having matched archival tissue available for whole-genome sequencing (WGS; n = 46). Cox-based elastic net regression models were used to identify and rank combinations of mutations by their ability to predict survival hazard. **Results:** Long-term follow up analysis demonstrated no significant difference in median overall survival (mOS) between pts randomized to G+N+D+T *vs* G+N (9.8 *vs* 8.8 months; hazard ratio (HR) = 0.88; p = 0.46). Median progression-free survival (mPFS) was also not significantly different between treatment arms (5.5 *vs* 5.4 months, respectively; HR = 0.95, p = 0.77). Landmark analysis demonstrated 4-year survivorship of 5.4% in pts treated with G+N+D+T arm compared to 1.6% with G+N (p = 0.07). Two or more ctDNA-based mutations (somatic and germline considered separately) in DNA damage repair (DDR) genes *BRCA1*, *POLE*, *ATM* or *FANCA* was present in 18/173 pts (10.4%) and was associated with improved OS with G+N+D+T *vs* G+N (mOS 26.2 months vs. 7.1 months; HR = 0.22 [0.07-0.7]; p = 0.0041, p-interaction = 0.012) as well as PFS (mPFS 14.6 vs. 4.6; HR = 0.17 [0.05-0.6]; p = 0.0020, p-interaction = 0.0070). In pts treated with G+N+D+T, partial response (PR) was seen in 63.6% of pts with ≥2 DDR gene mutations compared to 26.9% in other pts (p = 0.033), and this effect was not observed with G+N (p = 0.18). The DDR gene biomarker was validated in 5/6 (83%) biomarker-positive samples using archival tissue WGS. **Conclusions:** The presence of ≥2 DDR gene mutations was strongly associated with benefit from the combination of chemotherapy with dual immune checkpoint inhibitor therapy, and pts with this signature had prolonged mOS of over 2 years. This represents the first prospective study in PDAC to define a predictive biomarker beyond mismatch repair deficiency for benefit from immune checkpoint therapy. Given the long-term survival noted in this subgroup, assessment of DDR gene mutations could be considered as part of routine standard of care testing for mPDAC pts. Clinical trial information: NCT02879318. Research Sponsor: Predicine; Astra Zeneca; Canadian Cancer Trials Group.

Clinical outcomes and molecular characteristics of patients with metastatic pancreatic ductal adenocarcinoma according to involved metastatic sites.

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Background: It is well documented that Pancreatic ductal adenocarcinoma (PDAC) metastasize to the liver had worse outcome than to the lung, but the molecular basis was less clear. We employ a large Real-World Evidence dataset to evaluate clinical and molecular features of PDAC according to involved metastatic sites. **Methods:** The Foundry software platform was used to query electronic medical records of patients with metastatic PDAC who underwent Next-Generation Sequencing (NGS) at MD Anderson. Involved metastatic sites were extracted using natural language process from imaging reports then manually verified. Overall survival (OS) was calculated from date of diagnosis. **Results:** We identified 1,095 patients with metastatic PDAC diagnosed between May 2003 and Oct 2024. Median follow up was 41.8 months and median OS was 22.8 (95%CI: 20.2-25.2) months. Most patients (52.9%) had multiple metastatic sites including liver, 28.5% had liver only metastases, while 8.7% had lung only metastases. 10% had metastases not including liver. Patients with lung only metastasis had the best outcomes (median = 57.6 months, HR = 0.37 relative to liver only, 95%CI = 0.27-0.52, p = 9.3e-9), followed by patients with metastases not involving liver (median = 41.3 months, HR = 0.65, 95%CI = 0.49-0.87, p = 0.003). Patients with liver only metastasis (median OS = 19.5 months) had similar survival to those with multiple sites including liver (median = 19.3 months, HR = 1.1, 95%CI = 0.96-1.4, p = 0.13). *TP53* was more frequently mutated in patients with liver only metastasis (84%) and multiple metastases including liver (85%) compared to patients with lung only (73%) and multiple sites not including liver (67%, p = 9.3e-5). *GNAS* showed lower frequency (5%) in patients with liver only and patients with multiple metastasis including liver (2%) compared to patients with lung only (8%) or non-liver metastases (10%, p = 0.003). In patients with liquid biopsy (n = 240), lung only metastasis showed significantly lower positivity rate for mutation detection (50% vs 65% for liver only, 62% for other or multiple not including liver and 79% for multiple including liver, p = 0.009), and lower *TP53* detection rate (23% for lung only vs 46% for liver only, p = 0.02). The frequency of *KRAS* mutation and mutant allele distribution were not significantly different in tissue NGS. However, patients with lung only metastasis showed significantly less frequent *KRAS* mutation detection by liquid biopsy (10% vs 52% in liver only metastasis, p = 9.6e-4). **Conclusions:** PDAC patients without liver metastasis have markedly improved OS relative to patients with liver metastasis, and lower rates of *TP53* mutation. Similar frequencies of *KRAS* mutation were found in different patients by tissue testing. However, patients with lung only metastasis had lower positivity rate of ctDNA, and lower detection rate of *KRAS* mutation by liquid biopsy. Research Sponsor: None.

Pancreatic cancer mortality trends (2018-2023): Exposing racial inequities in Michigan's cancer burden.

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Background: Pancreatic cancer remains one of the most aggressive malignancies, with Black individuals facing significantly worse outcomes and a younger age of onset. Despite overall survival improvements in cancer care, racial disparities in pancreatic cancer continue to widen. This study analyzes Michigan's diverse population to quantify disparities and identify actionable solutions for healthcare equity. **Methods:** This observational study analyzed pancreatic cancer mortality patterns across Michigan in adults aged 25 and older were retrieved from the CDC WONDER database (2018–2023) using ICD-10 codes for malignant neoplasm of the pancreas. Crude mortality rates (CMRs) and Age-adjusted mortality rates (AAMRs) per 100,000 were calculated by age, gender and race, with 95% confidence intervals (CI) for precision to assess racial disparities in mortality outcomes. Temporal trends and annual percentage changes (APCs) were analyzed using Joinpoint regression. **Results:** From 2018–2023, Michigan reported 10,162 pancreatic cancer deaths, with Black residents (14.1% of the population) accounting for 1,289 and White residents (who make up 78.9%) for 8,664 deaths. Overall, CMR was higher for White residents (18.26 per 100,000) than Black residents (15.21 per 100,000) who experienced a sharper rise in AAMR, increasing by 8.10% [14.36 (13.55–15.16)] compared to 4.92% [12.36 (12.10–12.63)] for White residents. For Black residents, CMRs increased with age, rising from 8.14 per 100,000 (45-54 years) to 105.78 per 100,000 (85+ years), peaking at 69.46 (65-74 years) and 95.37 (75-84 years). White residents had lower CMRs overall, starting at 1.48 per 100,000 (35-44 years) and gradually increasing to 115.28 per 100,000 in the 85+ group.In Washtenaw County, Black residents had a rate of 14.01 per 100,000 and White residents 15.79 per 100,000 with similar trends in Genesee, Wayne, and Ingham counties. Treatment inequities compounded these disparities: Black patients faced 38% lower odds of surgery, 45% longer delays for chemotherapy, and 27% lower clinical trial enrollment. These findings highlight significant racial disparities in pancreatic cancer mortality, treatment access, and outcomes, underscoring the need for targeted public health interventions. **Conclusions:** Our findings reveal significant racial disparities in pancreatic cancer outcomes in Michigan, with Black residents experiencing higher mortality rates and a younger age of death than White residents. These disparities reflect systemic barriers, including delayed diagnosis, fewer surgeries, and limited access to specialized care. Addressing these inequities requires bias training, targeted screening for high-risk Black populations, and expanded oncology services, while actionable solutions such as patient navigation and community-based screening programs can help bridge this healthcare gap and promote equity.
Research Sponsor: None.

Multimodal machine learning predictions of treatment response and survival in advanced pancreatic cancer from the COMPASS trial.

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Background: Pancreatic cancer is an aggressive malignancy with limited therapeutic options and a poor prognosis. Current approaches to prognostication are limited, especially in advanced disease. We explored whether machine learning integrating multi-modal data could predict outcomes in advanced pancreatic cancer. **Methods:** We developed and evaluated machine learning models predicting disease control rate and one-year survival from the COMPASS trial (NCT02750657). Data modalities included clinical features, histopathology, radiology, RNAseq, and whole-genome sequencing (WGS). After pre-processing, we applied LASSO and XGBoost to each modality and early and late fusion techniques. Hyperparameter tuning and performance assessment were performed using repeated nested cross-validation. The PurIST RNAseq classifier served as a baseline. Area under the curve (AUC) was the primary metric. **Results:** The cohort included 260 patients (105 female; median age 64 [IQR 58–70]; 141 treated with FOLFIRINOX, 97 with gemcitabine and nab-paclitaxel). 170 (65%) achieved disease control and 168 (65%) survived at least one year. The performance of the machine learning models is shown in the Table. Predictions from the unimodal models had limited correlation with each other (the maximum pairwise correlation averaged across folds was between clinical and histopathology models, 0.21). The late fusion models up-weighted data modalities with stronger unimodal performance. **Conclusions:** Multiple individual data modalities can predict outcomes in advanced pancreatic cancer, with PurIST serving as a strong baseline. Despite differing predictions across data modalities, multimodal integration did not improve prognostic performance in this cohort. Research Sponsor: Ontario Institute for Cancer Research; Princess Margaret Cancer Foundation; The Terry Fox Research Institute Marathon of Hope Cancer Centres Network.

AUC for the PurIST baseline, the top 2 unimodal models, and the best fusion model for each outcome.

Outcome	Data Modality	AUC (95% confidence interval)
Disease control	PurIST	0.69 (0.69, 0.70)
	Radiomics	0.75 (0.72, 0.79)
	RNAseq	0.71 (0.70, 0.72)
	Fusion (late)	0.71 (0.69, 0.73)
One-year survival	PurIST	0.63 (0.62, 0.63)
	DNA mutations	0.64 (0.61, 0.66)
	RNAseq	0.57 (0.55, 0.60)
	Fusion (early)	0.61 (0.56, 0.66)

Integrative analysis of tumor microenvironment in advanced pancreatic cancer: Unraveling genomic and immune landscape for targeted therapies.

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Background: An understanding of genotype and immunophenotype interactions in advanced pancreatic ductal adenocarcinoma (PDAC) is important in designing combination strategies. In addition, PDAC subtypes may harbor unique tumor immune microenvironments (TMEs) and confer differential sensitivity to *KRAS* inhibitors (KRASi). We aimed to characterize the baseline TME in advanced PDAC and its relationship with genomic, transcriptomic and clinical data. **Methods:** The COMPASS trial (NCT02750657) investigated whole genome (WGS) and transcriptome (RNA-Seq) sequencing in patients (pts) receiving first line therapy for advanced PDAC. We performed multiplex immunohistochemistry (mIHC) to identify 5 immune cell subtypes (CD8+/CD4+ T cells, Tregs, B cells and macrophages) and CIBERSORT, a deconvolution method that uses gene expression profiles. Statistical analyses were performed using STATA/R software and significance was defined as $p\text{-}value < 0.05$. Multivariate logistic regression was used and Kaplan Meier analyses evaluated impact on survival. **Results:** Of 268 pts, 62 had available tissue samples with mIHC, WGS, and RNA-Seq data (n = 21 primary biopsies, n = 41 metastases, 34/41 liver). All 62 pts had *KRAS* mutations (28 G12D, 19 G12V, 10 G12R, 5 other) and 29 had *KRAS* major or minor imbalances. 55 cases (88.7%) were classified as classical subtype and HRDetect^{hi} was seen in 10 pts, including 5 with *BRCA1/2* mutations (4 germline, 1 somatic). In the overall cohort, differences between tumor and stroma were evident with increased infiltration of CD8 and CD4 Tcells and Tregs in stroma ($p< 0.001$) and increased macrophages (p= 0.0343) in tumor. CIBERSORT in a subset of 51 pts demonstrated increased M0 (p= 0.0035) and M2 macrophages (p= 0.0067) in liver metastases compared to primary samples, suggesting a more immunosuppressive TME. A higher number of B cells were seen in lung metastases (median 207.5 vs. 43.2 vs. 3.7 vs. 1.8 cells/mm2, p= 0.011) compared to abdominal wall, peritoneum and liver, respectively. Pts with *KRAS* major imbalance (n =14, 3 basal like) were found to have higher median numbers of CD8+ (114.5 vs. 25.1 vs. 27.5 cells/mm2, p= 0.038) and CD4+ Tcells (292.1 vs 133.4 vs. 97.4 cells/mm2, p= 0.005) when compared to minor/balanced samples, respectively. Basal-like PDAC had fewer macrophages than classical subtype (median 13.2 vs. 28.2 cells/mm2, p= 0.0103). On survival analysis, pts with HRDetect^{lo} and classical subtype with higher macrophage counts had a tendency towards increased survival (median OS: 11.8 vs. 9.5 months, p= 0.066). **Conclusions:** We identified increased CD8/CD4 T cell infiltration in PDAC stroma, as well as in pts with *KRAS* major imbalance. Immune cell profiling may complement molecular profiling as potential biomarkers and warrants further study in this context. Research Sponsor: PM2C/MOHCCN.

BRCA1/2 and *PALB2* short variants (SVs) contributed by clonal hematopoiesis (CH) in liquid biopsies (LBx) from patients with advanced pancreatic cancer (PC).

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Background: CH results from fitness-enhancing mutations in hematopoietic stem cells. Many CH somatic variants (SVs) are in cancer-associated genes, including *ATM* and *CHEK2*, which do not have a homologous recombination deficiency (HRD) phenotype. SVs in well-established HRD-associated genes like *BRCA1/2* and *PALB2* also appear in white blood cells as CH, albeit more rarely. Herein, we report the prevalence of SVs of CH origin in these clinically relevant genes that confound results of PC liquid biopsies (LBx) and study their association with HRD in tissue biopsies from the same patients. **Methods:** This study uses a novel variant origin prediction algorithm to classify the origin of each SV detected by FoundationOneLiquid CDx as germline, tumor-somatic, or CH, using a combination of sample-specific and dataset-learned features including fragmentomics (trained and validated against white blood cell standard). 5,625 PC LBx sequenced during routine clinical care was used for broad prevalence data. A subset with matched tissue biopsies (TBx, n = 536) was used to compare SV detection and true HRD via HRDsig in TBx, a signature validated to predict response to PARP inhibitors across multiple cancer types. **Results:** Among 303 PC LBx with a *BRCA1/BRCA2/PALB2* SV, 52 (17.2%) were predicted to be of CH origin. This percentage is larger than for other *BRCA*-associated canonical cancer types: prostate (14.1%, 139/980), breast (9.7%, 87/902), ovarian (7.0%, 14/200), but less than some non-canonical cancer types (Table). In PC patients with both LBx and TBx available, 29/536 (5.4%) had an SV in *BRCA1/BRCA2/PALB2* detected in LBx: 8/29 in LBx only; 21/29 in both LBx and TBx. 19/29 were predicted germline by the algorithm, were all also detected in TBx, and 15 (79%) of these TBx were HRDsig+. 5/29 (17%) were predicted to be tumor-somatic; two of these were detected in TBx and one (20%) was HRDsig+. Predicted CH SVs were detected in another 5 LBx (4 *BRCA2*; 1 *PALB2*). None of these were detected in TBx and none of the tumors were HRDsig+. **Conclusions:** While the majority (58%) of *BRCA1/BRCA2/PALB2* SV+ PC LBx harbored a predicted germline SV, 25% harbored tumor-somatic SV and 17% had SV exclusively predicted as CH-derived. Determining the cellular origin of *BRCA1/BRCA2/PALB2* in PC is essential given the potential impact on treatment selection. Research Sponsor: Foundation Medicine.

Cancer type	LBx, N	n with SV in *BRCA1/2/PALB2* (%)	% Germline SV present	% Tumor somatic SV present	% No germline/tumor somatic SV, only CH SV present
Lung	21456	928 (4.3)	25.5	51.3	23.1
Cholangiocarcinoma	1787	90 (5)	38.9	38.9	22.2
Pancreas	5625	303 (5.4)	57.8	25.1	17.2
Esophagus	1199	56 (4.7)	33.9	50.0	14.3
Prostate	13858	980 (7.1)	39.3	46.5	14.2
Colorectal	6639	391 (5.9)	15.3	73.4	11.0
Breast	11397	902 (7.9)	55.2	35.1	9.6
Ovarian	1464	200 (13.7)	66.0	27.0	7.0
Endometrial	795	84 (10.6)	20.2	73.8	6.0

5-FU + Naliri, gemcitabine plus nab-paclitaxel or both regimens given sequentially for first line treatment of metastatic pancreatic ductal adenocarcinoma: A randomized phase II comparative study (FUNGEMAX-PRODIGE 61).

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Background: New chemotherapeutic approaches are still needed to improve survival and quality of life in metastatic pancreatic ductal adenocarcinoma (mPDAC). We have previously published results of two randomized phase II of first-line sequential treatment strategies of intensified FOLFIRI regimen followed by gemcitabine-based regimens (FIRGEM and FIRGEMAX-PRODIGE 37 studies) with good efficacy and tolerability results. FUNGEMAX-PRODIGE 61 evaluated 5FU + Naliri (NAPOLI) vs gemcitabine + Nab-paclitaxel (MPACT) vs both regimens sequentially. **Methods:** Chemotherapy-naive pts with proven mPDAC, bilirubin levels < 1.5 ULN and performance status (PS) 0-1 were randomized to receive either the NAPOLI regimen for 2 months, alternating with the MPACT regimen for 2 months (arm A), NAPOLI alone (arm B) or MPACT alone (arm C) until progression or limiting toxicity. Using the Schoenfeld method, the primary endpoint was the progression-free survival (PFS) rate at 6 months from (H0) 30% over (H1) 45%, requiring 96 patients per arm (assuming 5% lost to follow-up). **Results:** Between 11/2018 and 01/2024, 288 pts were enrolled in 31 French centers and 283 included in the modified intent to treat population (mITT, patients who received at least one dose of treatment). Database lock was done on the 20/12/2024. Baseline characteristics were well balanced between the arm A, B and C (mean age: 65/63/65, female: 47/43/47%, PS-0: 33/34/37%, > 1 metastatic site: 53/48/48%, mean albumin 39/40/39 g/L). With a median follow-up of 39.2 months, study treatment was discontinued in 89.5%, 96.8% and 93.7% of patients for arms A/B/C; median treatment duration were 6.3/3.3/5.3 months, respectively. In the mITT, neither treatment with MPACT/NAPOLI (HR = 0.76, 95%CI: 0.57-1.02; p = 0.07) nor NAPOLI (HR = 1.20, 95%CI: 0.90-1.60; p = 0.22) lead to a statistically significant improvement of PFS over MPACT. PFS, Overall survival (OS) and safety data are summarized in the table. **Conclusions:** The study did not show superiority of either the sequence MPACT/NAPOLI or NAPOLI over standard MPACT. However, the sequential MPACT/NAPOLI regimen is feasible, tolerable, and associated with higher rates of 12-mo PFS and 24-mo OS and less neuropathy and can be considered in patients unfit to receive FOLFIRINOX. NCT03693677. Clinical trial information: 2024-518143-38-00. Research Sponsor: None.

	Arm A (MPACT/ NAPOLI)		Arm B (NAPOLI)		Arm C (MPACT)	
PFS						
median (mo)	6.2 [4.0;7.8]		3.7 [2.2;5.1]		5.7 [4.0;6.5]	
rate at 6-m	51.6% [41.1;61.0]		32.3% [23.04;41.81]		45.3% [35.1;55.0]	
rate at 12-m	20.3% [12.9;29.0]		12.7% [6.8;20.3]		11.9% [6.3;19.4]	
OS						
median (mo)	11.6 [8.4;15.0]		9.1 [7.10;10.45]		12.4 [9.76;14.03]	
rate at 24-m	23.8% [15.4;33.2]		9.5% [4.19;17.36]		12.5% [6.28;20.93]	
Grade 3-4 toxicities						
AE/SAE	**All Grades**	**Grade 3-4**	**All Grades**	**Grade 3-4**	**All Grades**	**Grade 3-4**
Neutropenia	25.3%	9.5%	11.8%	0%	26.3%	7.4%
Diarrhea	80%	17.9%	69.9%	16.1%	55.8%	5.3%
Vomiting	80%	15.8%	72%	14.0%	61.1%	4.2%
Peripheral Neuropathy	44.2%	5.3%	10.8%	0%	57.9%	8.4%

Machine learning and statistical prediction of overall survival (OS) from pre-dose plasma biomarkers in a randomized phase 2 trial (1801 Part 3B) of the GSK-3 inhibitor elraglusib in metastatic pancreatic ductal adenocarcinoma (mPDAC): Application toward patient enrichment.

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Background: Elraglusib is a first-in-class inhibitor of GSK-3ß, a well-credentialed target in cancer implicated in intrinsic oncologic processes and tumor immune response. Preliminary results of the 1801 Part 3B trial (NCT03678883) showed statistically significant benefits for elraglusib+GnP versus GnP for 1-year survival and mOS in mPDAC (companion abstract: Mahalingam et al.). We investigated plasma levels of cytokines/chemokines/soluble cell receptors/growth factors (CCSG) as potential biomarkers of favorable outcomes on elraglusib. **Methods:** Forty CCSGs were evaluated in pre-dose plasma from patients with previously untreated mPDAC enrolled in 1801 Part 3B treated with GnP (n = 78) or elraglusib+GnP (n = 155) using a Luminex immunoassay. Using Kaplan-Meier statistics and cutpoint determination, CCSGs were assessed for OS predictive ability in the elraglusib+GnP arm. Multivariate models were constructed to predict binarized survival at 12 months using machine learning (ML). Fivefold cross-validation was used in both analyses, and all methods were applied to the GnP arm to identify elraglusib+GnP specific predictors. **Results:** Data shown as of November 15, 2024. Multiple CCSGs significantly stratified elraglusib+GnP patients. The most extreme prognosticators were IFN-ß (average HR = 2.34), and PD-L1 (average HR = 0.52) (HR shown as high CCSG vs low CCSG). Screening of different ML approaches ranked logistic regression at the top, and hyperparameter grid search identified stochastic gradient solver with ridge regularization as the optimal method. The model had an accuracy of 88% (SD: 3.9%) and a balanced accuracy of 80% (SD: 8.5%). IFN-beta had the most substantial effect size (odds ratio (OR) = 72.28), followed by IL-18 (OR = 23.38) and PD-L1 (OR = 15.32). All other CCSGs had an OR between 0.03 and 6.71. When this model was applied to patients in the GnP arm, accuracy was 68.4%, and balanced accuracy was 43.1%. **Conclusions:** Many CCSG biomarkers were identified as promising predictors of survival benefit in mPDAC patients treated with elraglusib+GnP. Both univariate statistical and multivariate ML approaches show predictive significance with high interpretability. The initial ML model is specific to elraglusib treatment, not GnP alone. These results indicate that patients' initial immune state plays a role in response to elraglusib+GnP. However, single CCSGs for enrichment currently exclude too many patients ($>$ 75%), and thus, panels of biomarkers are being investigated with ML to overcome this limitation. The 1801 Part 3B clinical trial recruitment has been completed, and updated biomarker models reflective of topline OS data, available by April 2025, will be presented. Research Sponsor: Actuate Therapeutics Inc.

Real-world predictors of adverse clinical outcomes in pancreatic cancer using a machine-learning framework.

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Background: Completion of chemotherapy is crucial for clinical benefit and has been linked to improved outcomes, but is often challenging given the toxicities of chemotherapy regimens. The main treatment regimen for pancreatic adenocarcinoma (PDA), FOLFIRINOX (FFX), is highly toxic, requires frequent dose-modifications, and most patients are too sick to tolerate multiple lines of therapy. Given the aggressiveness of the disease, selecting the appropriate first-line dosing is crucial as it can be associated with better patient outcomes. The current study objective is to evaluate the association between real-world dosing patterns and clinical toxicity using a machine-learning framework. **Methods:** Patients attending GI oncology clinics at University of California, San Francisco between November 2011 – December 2023 with a documented administration of FFX were included. Predictors of clinical outcomes included baseline demographic and clinical features, cycle-specific laboratory data, and dosing information for FFX sub-components. Group-based 5-fold cross-validation for logistic regression, random forest, and XGBoost models were used to identify features associated with clinical outcomes (anemia, dehydration, nausea/vomiting, neutropenia, and polyneuropathy). Model performance was evaluated using AUC. **Results:** Data for 505 patients with PDA receiving FFX across 5,041 cycles were included.The random forest models yielded the best fit for the prediction across all outcomes (Table). Key features consistently associated with outcomes included cycle number, cumulative dose of drug received, laboratory data (PT, INR, albumin), patient demographics (male sex, race, and smoking status), and clinical features, such as hypertension. **Conclusions:** Our study identifies clinical features in combination chemotherapy leading to specific toxicities, highlighting these as ideal strategies for intervention. Early prognostic indicators of adverse outcomes can guide early management for high-risk individuals through supportive measures and dose modification, before high-grade toxicities and discontinuations wherein patients can no longer benefit from therapy. Research Sponsor: UCSF Pancreas Center.

Summary of FOLFIRINOX model outputs across clinical outcomes.

Outcome\Model	Logistic Regression	Random Forest	XGBoost	Key Features
Anemia	0.61 ± 0.03	0.67 ± 0.03	0.62 ± 0.04	[1] INR [2] Irinotecan dose [3] Any polyneuropathy
Dehydration	0.64 ± 0.03	0.72 ± 0.02	0.68 ± 0.05	[1] Cumulative irinotecan [2] Cumulative oxaliplatin [3] Cumulative fluorouracil
Nausea or vomiting	0.62 ± 0.04	0.68 ± 0.03	0.66 ± 0.03	[1] Cumulative irinotecan [2] Cumulative oxaliplatin [3] Cumulative fluorouracil
Neutropenia	0.57 ± 0.04	0.61 ± 0.06	0.61 ± 0.01	[1] Male sex [2] Cumulative fluorouracil [3] Smoking status – never
Polyneuropathy	0.53 ± 0.06	0.53± 0.06	0.52 ± 0.04	[1] Male sex [2] Oxaliplatin [3] Constipation

4187 Poster Session

A PBMC and machine learning based biomarker signature to predict second line chemotherapy success in advanced PDAC: Translational data of the PREDICT trial—A prospective, multicenter, trial of the AIO Pancreatic Cancer Group (AIO-PAK-0216).

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Background: The PREDICT trial, a recent phase IIIb/IV study, aimed to address the critical need for improved personalized treatment strategies in advanced pancreatic cancer. This translational investigation examined the predictive value of 1st line chemotherapy (CTX) response on the efficacy of subsequent 2nd line treatment by using liquid biomarkers combined with machine learning (ML). **Methods:** Pts. were stratified into two cohorts based on short or long 2nd line CTX time to treatment failure (S-/L-TTF2; *n* = 10 per group, 80/20% quantiles). Treatment-naïve PDAC tissue specimens underwent laser microdissection for tumor cell enrichment, followed by RNA profiling using NanoString™ PanCancer IO360. Selected differentially regulated genes from the omics results were utilized to screen peripheral blood mononuclear cells (PBMCs) from 2nd line treatment-naïve patients at protein (flow cytometry, FC) or RNA (RT-qPCR) levels. FC data was analyzed using R-based single-cell clustering (x-Shift, FlowSOM, T-REX) to generate HyperGates (HGs), with subsequent ML-based backgating (HyperFinder algorithm) of the most differential clusters. Additionally, classical ManualGates (MGs) were generated. Feature selection employed the Weka-based WrapperSubsetEval (WSE) algorithm with eight different classifiers (NB, KLR, LR, SMO, IBk, RT, RF, J48). The classifier/subset with optimal performance was utilized for binary classification (S-TTF2 vs. L-TTF2) of training (80%, n = 66) and validation (20%, n = 16) datasets. **Results:** Transcriptome analysis of L- vs. S-TTF2 tumor tissues revealed increased inflammation (upregulated 18-gene signature), immune cell activation/infiltration (e.g. CD4/CD8 T cells), and immune exhaustion (upregulation of e.g. PDCD1, LAG3, CTLA4, TIGIT) in L-TTF tumors. Further, the favorable Bailey immunogenic subtype was enriched in the L-TTF2 group. Analysis of eight FC panels (19 candidates) revealed 1198 differential clusters with HGs and 881 classical MGs. Feature selection, combining FC data with RT-qPCR results and clinical parameters, identified a best performing signature of 5 HGs and 2 MGs for 7 protein markers (CXCR4, CD8, CD4, CD62P, CD307b, CD45, CD121b). ML using a kernel logistic regression successfully predicted S- and L-TTF2 binary groups prior to 2nd line CTX with nal-IRI/5-FU/LV (ROC-AUC $>$ 0.90 for training and validation). **Conclusions:** We identified a favorable tumor immune microenvironment in L-TTF aPDAC patients, characterized by CD8 T cell-inflamed ("hot") tumor tissues prior to 2nd line CTX. A 7-marker liquid biomarker panel, comprising 7 flow cytometry PBMC population gates, was developed for early prediction of 2nd line nal-IRI/5-FU/LV CTX success. These findings aim to advance personalized treatment strategies. Clinical trial information: NCT03468335. Research Sponsor: Servier.

Preliminary result of a phase Ib study: Efficacy and safety of FG-M108 plus gemcitabine and nab-paclitaxel in patients with Claudin18.2-positive, locally advanced, unresectable, or metastatic pancreatic cancer.

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Background: FG-M108, an ADCC-enhanced anti-CLDN18.2 monoclonal antibody, showed significant efficacy in first-line (1L) treatment of gastric cancer. Herein, we report the safety and efficacy results of FG-M108 in 1L treatment of pancreatic cancer (cohort C2 and D2). **Methods:** In this open-label, multicenter phase I/II study patients received FG-M108 (cohort C2: 300mg/m2 or cohort D2: 600mg/m2 Q3W) plus gemcitabine (1000mg/m2, d1, d8, Q3W) and nab-paclitaxel (125mg/m2, d1, d8, Q3W). Eligible patients were those with CLDN18.2 positive local advanced or metastatic pancreatic cancer who were previously untreated. The primary endpoint were the incidence of adverse events (AEs) and preliminary clinical efficacy (ORR, DCR, DOR, PFS, and OS). **Results:** As of November 15, 2024, 50 patients were enrolled and received FG-M108+gemcitabine/nab-paclitaxel treatment (39 patients in cohort C2, 11 patients in cohort D2). The median age was 61 (range 30-72). 47 (94%) patients were with CLDN18.2 moderate-high expression. Out of 50 patients, 44 patients had at least one tumor assessment after baseline and included in the efficacy analysis set. The median follow-up time (95%CI) for the 32 patients with CLDN18.2 moderate-high expression was 9.5 months (6.8,11.2) , with a maximum treatment duration of 13 months. In the subgroup of cohort C2 patients with CLDN18.2 moderate-high expression assessed by Independent Review Committee(IRC)—16 patients achieved confirmed PR, and one achieved unconfirmed PR. ORR was 53.1% (34.7,70.9), and DCR was 100.0% (89.1-100.0). The median DOR reached 9.9 months (7.8,NE), and the median PFS reached 9.9 months (7.0,NE) . OS data are not yet mature, with 23 patients still alive, achieving a median OS of 17.4 months (11.0,NE). Treatment-emergent adverse events (TEAE) occurred in 32 patients (100.0%), in which 15 (46.9%) were ≥ grade 3. The most common FG-M108 related AEs in cohort C2 & D2 were nausea (56.4% vs 36.4%), vomiting (48.7% vs 45.5%), and hypoalbuminaemia (46.2% vs 54.5%). **Conclusions:** The combined therapy of FG-M108 plus chemotherapy as 1L treatment for patients with CLDN18.2 positive pancreatic cancer was generally well tolerated with promising survival (PFS and OS) data especially in patients with CLDN18.2 moderate-high expression, pivatol phase III clinical study will start in 2025 Q2. Clinical trial information: NCT04894825. Research Sponsor: None.

4189 Poster Session

Neo-adjuvant chemo-immunotherapy in pancreatic cancer: Results of the Australasian Gastrointestinal Trials Group (AGITG) NEO-IMPACT pilot trial.

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Background: Despite curative intent surgery and peri-operative chemotherapy for resectable pancreatic ductal adenocarcinoma (PDAC), recurrence rate remains high (>80%). Whilst immunotherapy has not been shown to be effective in the metastatic setting, there may be a scientific rationale for mobilising the immune system before surgery for localised disease to improve outcomes. **Methods:** NEO-IMPACT is a single arm phase II study testing the feasibility and safety of delivering 12 weeks of neoadjuvant immune checkpoint inhibitor in combination with FOLFIRINOX (3 doses of 1500mg durvalumab q28d + 6 cycles of FOLFIRINOX q14d) for resectable or borderline resectable pancreas cancer. The patients then received 3 months of adjuvant chemotherapy. The primary endpoint was the proportion of patients receiving ≥80% of planned neoadjuvant treatment. A sample size of 20 was calculated to allow 80% power. Secondary endpoints include the proportion of patients missing surgery due to treatment related adverse events (TRAEs); treatment tolerability; R0 resection rate; pathological complete response rate; objective response rate. **Results:** 20 patients with PDAC were enrolled between August 2022 and June 2024, 13 resectable and 7 borderline resectable disease. 17 of 20 patients (85%) completed planned neoadjuvant treatment. Grade 3-4 adverse events (AEs) occurred in 8 patients. The most common was infection (4), febrile neutropenia (1) and nausea (2). 1 patient died from 5FU toxicity due to homozygous loss of DPYD. There were 2 iAEs (colitis and maculopapular rash). 1 patient had TRAE and had to come off trial but proceeded to surgery. 3 patients (1 borderline/2 resectable) became unresectable at assessment for surgery following neoadjuvant therapy. Of the 16 patients who underwent surgery (12 head; 4 neck/tail), 2 had a complete pathological response. 13 had an R0 resection; 3 had an R1 resection. All 16 patients received post operative adjuvant therapy. At a median follow up of 15 months, 5 patients who proceeded to surgery and adjuvant therapy have recurred. **Conclusions:** Neoadjuvant chemoimmunotherapy is feasible and safe for patients with resectable and borderline resectable pancreas cancer. A 10% CPR rate and 70% R0 resection rate are encouraging, and this approach should be further explored in a larger population. Clinical trial information: ACTRN12622000378729. Research Sponsor: GI cancer.org.au (Australasian Gastrointestinal Trials Group); Astra Zeneca Pty Ltd.

NeoOPTIMIZE: Phase II trial of adaptive switching of neoadjuvant FOLFIRINOX (FFX) to gemcitabine/nab-paclitaxel (GA) resectable/borderline resectable (BR)/ locally advanced (LA) pancreatic adenocarcinoma (PDAC).

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Background: Neoadjuvant chemotherapy (NAC) for localized PDAC may improve R0 resection. FFX and GA are used but lack of predictive biomarkers remains a barrier to optimal NAC. The angiotensin-II receptor blocker (ARB), losartan, remodels vascular perfusion to enhance NAC efficacy. We established an experimental platform for dynamic switching of NAC +/- radiation therapy for resectable/BR PDAC and an exploratory cohort of LA PDAC. **Methods:** Patients (pts) received 4 cycles of FFX (ox 85 mg/m2; LV 400 mg/m2; iri 150 mg/m2; 5-FU 2400 mg/m2), then were restaged in a multi-disciplinary tumor board (Restage I). Pts without progression (CT and CA19-9 increase <30% from baseline) completed 4 more cycles of FFX. If there was progression (CT and/or CA19-9 increase > 30%) or intolerance, pts were switched to GA (nab-P 125 mg/m2; gem 1000 mg/m2) for 2 months. After a total of 4 months NAC, pts were re-staged (Restage 2) and had surgery or chemoRT (if vascular involvement) then surgery. Losartan (50mg QD) was given throughout NAC/chemoRT. The primary endpoint was the proportion of resectable/BR with R0 resection. **Results:** Of 43 patients screened,16 were resectable, 21 BR, 5 LA and 1 ineligible. Median age was 65 years (range: 34-80), 49% male, 84% Caucasian white. Head of pancreas primary was 84%. Mean baseline CA19-9 96 ng/mL. 1 pt had progressive disease prior to Restage 1. Of the 36 pts at Restage 1, 31 continued FFX and 5 switched to GA. 18 patients on FFX had a radiographic response, 5 had CA 19-9 decrease >25%, and 8 had stable disease with unchanged CA 19-9. 3 pts switched to GA for radiographic progression,1 for increased CA 19-9 >30% and 1 for FFX intolerance. Of 34 pts evaluated at Restage 2, 2 continued NAC, 13 had pre-op chemoRT (12 BR and 1 resectable), and 19 proceeded to surgery. 24/27 (88%) pts on FFX had R0 resections; 4/4 (100%) pts switching to GA had R0 resections. Overall, 77% pts completing NAC FFX had R0 resections; 80% pts switched to GA had R0 resections. Grade > 3 toxicities 7% FFX and 5% GA. **Conclusions:** Early switching to GA in pts progressing on FFX led to an equivalent R0 resection rate. Optimization of NAC made it possible to undergo curative intent surgery that would not have occurred. Secondary endpoints of DFS, OS and multiomic based studies of blood and tumor tissue via our Serial Measurements of Molecular and Architectural Responses to Therapy (SMMART) platform are underway to identify molecular markers to predict response and determine whether a switch in treatment is indicated. Clinical trial information: NCT04539808. Research Sponsor: None.

4191 Poster Session

Development and prospective validation of a novel cfDNA-based diagnostic model for the early detection of pancreatic cancer.

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Background: Pancreatic cancer (PC) is one of the most lethal malignancies, with a 5-year survival rate below 10%, primarily due to late-stage diagnosis. Existing diagnostic markers, like CA19-9, show inadequate sensitivity and specificity for early detection. To address this critical gap in early PC detection, this study developed and prospectively validated a cfDNA-based diagnostic model integrating fragmentomics features, including copy number variations (CNVs), fragment size ratios (FSR), and orientation-aware cfDNA fragmentation (OCF). **Methods:** A multicenter study was carried out with a case-control cohort (n = 467) for model development and a prospective cohort (n = 1,926) for clinical validation. Plasma cfDNA underwent low-pass whole-genome sequencing to extract fragmentomics features like CNVs, FSR, and OCF. A stacked ensemble machine-learning model was built based on case-control data and validated in the prospective cohort of PC elevated-risk individuals with diabetes or obesity. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were evaluated and compared with those of CA19-9. The follow-up was intended to last for 3 to 5 years, with the current follow-up period ranging from 12 to 24 months. **Results:** In the case-control cohort, the cfDNA-based model achieved AUCs of 0.9799 and 0.9622 in the training and validation sets, respectively, with both sensitivity and specificity exceeding 90%. In the prospective cohort (n = 1,926), for the 8 PC cases identified, the cfDNA model demonstrated a sensitivity of 75%, specificity of 98.1%, and PPV of 15.2% for detecting PC, significantly outperforming CA19-9 (sensitivity: 12.5%, specificity: 94.3%, PPV: 0.9%). Notably, the cfDNA model detected all 3 Stage 0 cases, 1 of 3 Stage I cases, and both Stage II cases, providing a median lead time of 227.5 days (range: 45–298 days) compared to imaging modalities. In contrast, CA19-9 detected only one Stage II case out of eight confirmed PC cases (12.5%). The model demonstrated significant potential in stratifying pancreatic cysts into high-risk and low-risk categories. While CA19-9 is ineffective in detecting either high-risk or benign cysts within the prospective cohort, the cfDNA model successfully differentiates between high-risk and low-risk pancreatic cysts (e.g., high-risk IPMN, 1/1 = 100% sensitivity; low-risk SCN, 0/1 = 0% false positive), which further underscores its clinical utility. **Conclusions:** This study is the first to validate a cfDNA-based diagnostic model for PC in a large elevated-risk population, showing superior performance and significant lead time benefits. The model detects PC earlier with much higher sensitivity and specificity than CA19-9, promising better outcomes with earlier treatment. The findings highlight cfDNA's potential for non-invasive PC screening in clinical settings. Research Sponsor: The National Key Research and Development Program of China; The Tianjin Key Medical Discipline (Specialty) Construction Project.

Prognostic value of postoperative circulating tumor DNA and tumor markers in resected pancreatic adenocarcinoma (PAAD): An interim analysis of a prospective observational study.

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Background: Despite the benefits of postoperative adjuvant chemotherapy, recurrence rates of PAAD remain as high as 60% within the first year, underscoring the need for improved strategies to optimize treatment plans. This prospective observational study aims to evaluate the potential of postoperative ctDNA-based minimal residual disease (MRD) as an early predictor of disease relapse in resected PAAD using next-generation sequencing. **Methods:** Pathologically confirmed stage I-III PAAD patients who underwent surgical resection and carried KRAS mutations were enrolled. Eligible criteria included negative surgical margins and no metastasis prior to adjuvant therapy. Patients who did not receive adjuvant therapy were excluded. Tumor tissue samples collected during surgery were analyzed using a 769-gene NGS panel, while plasma samples were obtained at landmark (4–8 weeks post-operation and pre-therapy), 12-, 24-, 36-, and 48-weeks post-operation, and 2 weeks post-adjuvant therapy. Plasma samples were assessed for MRD using MinerVa (Genecast Biotechnology). Concurrently, tumor biomarkers such as CA19-9 were measured. The primary endpoint was overall survival (OS), while the secondary endpoint was disease-free survival (DFS). The trial is designed for a total follow-up period of three years. **Results:** As of November 27, 2024, a total of 133 patients underwent MRD analysis. KRAS mutations were distributed as follows: p.G12D in 55%, p.G12V in 27%, p.G12R in 13% and other subtypes in 5%. Nine patients were excluded due to loss of follow-up, and 12 were excluded for less than six months of follow-up, leaving 112 patients for this interim analysis. MRD positivity rates were 16%, 9%, 10%, 15%, 11%, and 11% at landmark, 12, 24, 36, 48 weeks, and 2 weeks post-therapy, respectively. Landmark MRD positivity was a significant predictor of disease recurrence (HR = 2.39, 95%CI:1.14-5.01, p = 0.017). Combining landmark MRD with biomarker CA19-9 improved prognostic accuracy (HR = 2.70, 95%CI:1.4-5.5, p = 0.002). Patients with longitudinal MRD-positive (detected at any time point excluding landmark or relapse) had significant worse DFS (HR = 3.13, p = 0.001) and worse OS (HR = 0.73, p = 0.001) compared to those with negative MRD. Analysis of MRD status at landmark and week 36 revealed that patients transitioning from MRD-positive to MRD-negative (clearance) had significantly better DFS compared to those with persistent MRD positivity (p = 0.023). Notably, no patients deceased from the MRD clearance group. **Conclusions:** These findings underscore the clinical utility of integrating landmark and longitudinal MRD assessments with tumor markers for comprehensive risk stratification and prognostication in resected PAAD patients. This approach could potentially guide personalized treatment strategies and improve patient outcomes. Clinical trial information: NCT05479708. Research Sponsor: None.

Five-year outcomes of perioperative or only adjuvant gemcitabine plus nab-paclitaxel for resectable pancreatic cancer (the NEONAX trial): A randomized phase II trial of the AIO pancreatic cancer group.

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Background: Perioperative chemotherapy (CTX) in resectable pancreatic ductal adenocarcinoma (rPDAC) is still not considered standard of care and data are limited. NEONAX examined gemcitabine (Gem)/nab-paclitaxel (nab-P), in the perioperative or adjuvant therapy of resectable PDAC (NCCN criteria). **Methods:** NEONAX is a prospective, randomized phase II trial with two independent arms (127 patients, 22 German centers) and randomization 1:1 to perioperative (2 pre- and 4 postoperative cycles, po-arm A) or adjuvant (6 cycles, ad-arm B) of gem (1000mg/m2 BSA, d1, 8, 15) and nab-P (125mg/m2 BSA, d1, 8, 15), q4w. **Results:** As we previously reported were R0- and N0-resection rates high (po-R0 88%, ad-R0 67%, po-N0 33%, ad-N0 29%) in the ITT-population (all randomized pts.). The primary endpoint DFS rate of 55% @ 18 months in the mITT population (defined as R0/R1 resected pts. that either started perioperative (A) or adjuvant (B) CTX), was not reached in both arms (arm A: 32%, arm B 41%). Whereas 91.5% of pts. in po-arm A started and 84.7% completed neoadjuvant CTX, only 42.4% of pts. in ad-arm B started and 25% completed adj. CTX, so the CTX dose intensity was higher in the po-arm A. (Seufferlein et al., Ann Onc 2023) Here we report long-time 5-year outcomes according to PFS and OS and present a preplanned subgroup analysis of potential prognostic factors. The mOS in the ITT population (all randomized pts.) was 25.5 mo. in the po-arm and 16.8 mo. in the ad- arm. This corresponds to an mDFS of 11.4 mo. in the po-arm and 5.1 mo. in the ad-arm, respectively. The mOS in the mITT population (all randomized pts. that started po-ctx (po-arm) or started ad-ctx (ad-arm)) was 27.9 mo. in the po-arm and 26.8 mo. in the ad-arm. This corresponds to an mDFS of 14.1 mo. in the po-arm and 16.1 mo. in the ad-arm, respectively. In the preplanned analysis of subgroup factors impacting outcome, the benefit of po-treatment was independent of tumor size, N-status and baseline Ca19-9 level. This benefit was not visible in the mITT population where only patients in the ad-arm were included who had started adjuvant treatment postoperatively. **Conclusions:** These 5 year data confirm the outcome of patients receiving gem/nab in the po-setting in the ITT population. DFS and OS effect were numerically better compared to the ad-arm although the trial was not powered for direct comparison of the arms. This difference disappeared in the mITT population when patients received more CTX in the ad arm. We conclude that the difference between ITT and mITT is likely because more CTX could administered in the po-arm when the ITT population was considered and may constitute one of the major effects of neoadjuvant chemotherapy in resectable PDAC, particularly when a high rate of patients as in our multicenter trial could get neoadjuvant, but not adjuvant treatment. Clinical trial information: NCT02047513. Research Sponsor: Bristol Myers Squibb GmbH & Co. KGaA.

Perioperative pembrolizumab (pembro) plus chemotherapy (chemo) for locally advanced gastric or gastroesophageal junction (G/GEJ) cancer: Asia versus non-Asia subgroup analysis of KEYNOTE-585.

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Background: In the randomized phase 3 KEYNOTE-585 study (NCT03221426), pCR was significantly improved in participants (pts) with locally advanced G/GEJ cancer treated using perioperative pembro + chemo vs placebo (pbo) + chemo, although the difference in EFS did not meet the prespecified criteria for significance. We present an exploratory subgroup analysis by geographic region (Asia vs non-Asia). **Methods:** Eligible pts had untreated, locally advanced, resectable G/GEJ adenocarcinoma (including Siewert type 2 or 3 tumors). Pts enrolled in the main cohort (n = 804) received neoadjuvant pembro 200 mg IV Q3W or pbo + chemo (cisplatin + capecitabine or 5-FU) for 3 cycles (C); after surgery, pts received adjuvant pembro or pbo + chemo Q3W for 3C then adjuvant pembro or pbo Q3W for 11C. Pts in the FLOT cohort (n = 203) received neoadjuvant pembro 200 mg IV Q3W or pbo Q3W for 3C + FLOT Q2W for 4C; after surgery, pts received adjuvant pembro or pbo Q3W for 3C + FLOT Q2W for 4C, then adjuvant pembro or pbo Q3W for 11C. Primary end points were pCR (BICR), EFS (RECIST v1.1 by investigator), OS (main), and safety (FLOT). We report outcomes in the main and FLOT cohorts combined. The database cutoff date was February 16, 2024 (final analysis). **Results:** Of 1007 pts enrolled, 387 were enrolled in Asia; 620, at non-Asia sites; baseline characteristics were generally balanced, with notable exceptions for ECOG PS 1 (11.9% Asia vs 37.1% non-Asia), FLOT backbone (1.6% vs 31.8%), tumor location stomach (86.6% vs 68.9%), and tumor stage III-IVa (85.8% vs 74.0%). In the Asia subgroup, pCR was 17.1% with pembro + chemo vs 2.1% with pbo + chemo (difference, 15.0%; 95% CI, 9.7-21.2); median EFS was 69.8 mo vs 42.7 mo (HR, 0.81; 95% CI, 0.60-1.10), with a 5-year rate of 54.1% vs 45.6%; median OS was not reached (NR) vs NR (HR, 0.87; 95% CI, 0.63-1.19), with a 5-year rate of 61.3% vs 57.4%. In the non-Asia subgroup, pCR was 12.4% with pembro + chemo vs 3.3% with pbo + chemo (difference, 9.1%; 95% CI, 4.9-13.6); median EFS was 37.7 mo vs 24.3 mo (HR, 0.79; 95% CI, 0.64-0.98), with a 5-year rate of 44.0% vs 33.0%; median OS was 60.7 mo vs 42.4 (HR, 0.85; 95% CI, 0.68-1.06), with a 5-year rate of 50.5% vs 42.6%. In the Asia subgroup, treatment-related AE (TRAE) rates were 98.4% with pembro + chemo vs 97.4% with pbo + chemo; grade 3-5 TRAE rates were 69.6% vs 65.1%, respectively. In the non-Asia subgroup, TRAE rates were 94.1% with pembro + chemo vs 96.1% with pbo + chemo; grade 3-5 TRAE rates were 65.5% vs 61.7%, respectively. **Conclusions:** A favorable trend in EFS and OS was seen in both the Asia and the non-Asia subgroups of KENOTE-585; additional antitumor activity of pembro + chemo was consistently observed, regardless of region. The safety profiles were generally comparable between the subgroups. These findings support the global development of this perioperative immunotherapy/chemotherapy regimen. Clinical trial information: NCT03221426. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Association of neighborhood-level factors with access to genetic testing in patients with resectable pancreatic ductal adenocarcinoma.

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Background: Since 2019, the NCCN has recommended genetic testing for all patients with pancreatic ductal adenocarcinoma (PDAC). However, only one-third of patients undergo testing. For other cancers, social determinants of health have been shown to influence access to genetic testing. This study examines disparities in genetic testing among PDAC patients using neighborhood-level measures. **Methods:** We retrospectively analyzed 249 patients who underwent curative-intent resection for PDAC at a high-volume academic center between 2019 and 2023. Neighborhood disadvantage was quantified using the Area Deprivation Index (ADI). Additional socioeconomic variables included Rural-Urban Classification (RUCA) codes, insurance type (private vs. non-private), and distance to the treating facility. The primary outcome was completion of genetic testing. For those that did not undergo testing, we separately analysed the association between socioeconomic factors and presence of a referral for genetic counseling or testing. Logistic regression models adjusted for age, sex, and period of diagnosis were used to assess associations. **Results:** The cohort's mean age was 66.6 years (SD: 9.2); 45.1% were female, and 97.6% identified as non-Hispanic White. Median ADI was 55.0 (IQR: 29.5), and 38.1% lived in rural areas. Genetic testing was completed by 96 patients (40.1%), identifying pathogenic variants in 18 (18.7%). Multivariable analysis revealed age above 65, higher ADI, and greater distance from the facility significantly reduced testing likelihood. Testing rates increased between 2019 and 2023 (Table 1). Among the 153 patients without testing, only 41.2% were referred for genetic counseling/testing. Greater distance from the facility was associated with lower likelihood of being referred (OR: 0.33 [CI: 0.13, 0.85]). **Conclusions:** Neighborhood-level factors influence genetic testing access, even in a predominantly racially homogenous population. Targeted interventions are needed to reduce disparities and improve testing and referral rates. Research Sponsor: None.

Univariable and multivariable logistic regression for association of socioeconomic factors with completion of testing.

	Univariable	Multivariable*
Factor	**OR [95% CI]**	**OR [95% CI]**
ADI (continuous)	0.12 [0.04, 0.46]*	0.15 [0.02, 0.97]*
Urban residence (ref: Rural)	0.61 [0.34, 1.04]	0.97 [0.50, 1.90]
Distance to facility (ref: Low, <33)		
Moderate, 33–61	0.49 [0.26, 0.93]*	0.75 [0.34, 1.65]
High, ≥ 61	0.31 [0.17, 0.56]*	0.45 [0.21, 0.99]*
Age ≥ 65 (ref:<65)	0.81 [0.50, 1.31]	0.50 [0/26, 0.94]*
Female Sex (ref: Male)	1.05 [0.68, 1.62]	1.08 [0.57, 2.04]
Non-private insurance (ref: Private)	0.77 [0.46, 1.28]	1.13 [0.63, 2.01]
Period of diagnosis (ref: 2019-2020) 2023	7.32 [3.63, 14.78]*	7.37 [3.52, 15.43]*

*Statistically significant. Adjusted for age, sex, insurance status, and period of diagnosis.

Constructing genetic-immune prognostic subtypes of primary duodenal adenocarcinoma through whole exome sequencing and AI-assisted immune microenvironment analysis.

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Background: Primary duodenal adenocarcinoma (DA) is a rare gastrointestinal tumor with a poor prognosis. This study aimed to investigate the tumor immune microenvironment (TIME) and genetic landscape of DA to depict the unique DA subtypes, distinguishing its prognosis and identifying potential therapeutic targets. **Methods:** To reveal the heterogeneity of DA's genetic landscape and TIME, 88 treatment-naïve DA tumor samples were analyzed via multiplex immunofluorescence (mIF) staining, whole-exome sequencing, and RNA sequencing. The quantity of infiltrating cells, tertiary lymphoid structure, and spatial analysis was conducted using an automated platform (APTIME), an artificial intelligence-based analysis tool for analyzing pathology images from formalin-fixed paraffin-embedded slides stained with mIF. **Results:** Significant heterogeneity was observed in the genetic and immune landscapes of DA. A genetic-immune classification was established, identifying four distinct subtypes: MSI (microsatellite instable), InA(inflamed active), ML (macrophage-low), and MH (macrophage-high). The InA subtype exhibited high levels of infiltrating immune cells, while the MH subtype, characterized by enriched tumor-associated macrophages, was associated with the worst overall survival. The MH subtype frequently harbored TGF-β pathway mutations, particularly in SMAD4, while the ML subtype showed alterations that predominantly in the SWI/SNF pathway, specifically in ARID2. Spatial analysis indicated that closer proximity between macrophages and both tumor cells and T cells correlated with worse prognosis in DA patients. Closer interactions between PD-L1 and PD1+ T cells in the MH subtype suggested that PD-1/PD-L1 interactions contributed to an immunosuppressive tumor microenvironment. **Conclusions:** This study enhances the understanding of DA's molecular characteristics, particularly through the identification of a novel genetic-immune subtype, and provides a foundation for developing precision treatment strategies for this malignancy. Research Sponsor: None.

Uncovering the tumor microenvironment (TME): Exploring survival and immunotherapy (IO) response in cancer of unknown primary (CUP).

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Background: Cancer of Unknown Primary (CUP) is a group of rare and heterogeneous metastatic cancers with unidentifiable site of origin at time of diagnosis, despite extensive investigation. Characterization of CUP remains challenging, and biomarkers are urgently needed to better tailor therapies. Tumor microenvironment (TME) comprises the dynamic and complex network of extracellular matrix, blood vessels, immune cells, signaling molecules surrounding a tumor. It plays a critical role in tumorigenesis, progression and response to treatment. This study investigates the correlation between clinical factors, TME, IO and overall survival outcomes in patients diagnosed with CUP. **Methods:** We retrospectively evaluated 49 CUP patients who underwent Boston Gene Tumor Portrait (BGTP) testing between January 2023 and July 2024. BGTP utilizes a combination of Next-Generation Sequencing (NGS) and artificial intelligence to analyze a tumor sample's genetic profile along with its surrounding microenvironment, thereby providing a more comprehensive view to support clinical decision-making and optimize treatment strategies. Clinico-pathological data, including age, ECOG performance status at diagnosis, baseline laboratory results, tumor histology and grade, number of metastatic sites (NMS) and IO treatment history were collected through retrospective chart review. TME was categorized into 4 subtypes: immune-enriched (IE), immune-enriched/fibrotic (IE/F), fibrotic (F) and immune-depleted (D). **Results:** Baseline characteristics of 49 CUP patients show median age at diagnosis was 63 years (range 32-80). Most patients were male (59%). Grade was reported as poorly differentiated in 69%, with pathology described as carcinoma (47%), adenocarcinoma (33%), squamous cell carcinoma (10%) and malignant neoplasm (8%). TME subtypes distribution was 33% IE, 14% IE/F, 16% F, 37% D. Univariate analysis revealed that better outcomes were associated with lower NLR (< 5) (median survival 57 vs 11 months, p = 0.006), lower ECOG (57 vs 16 vs 6 months for ECOG 0, 1 and 2 respectively, p = 0.002), lower NMS (< 3) (45 vs 14 months, p = 0.046). Survival data of TME and NLR subsets is shown in the table. **Conclusions:** This is the first characterization of TME profile in CUP. A diverse range of TME subtypes were seen in this population. While classical prognostic factors such as NLR, ECOG, NMS were associated with better survival, there also appears to be a trend toward survival benefit with IO in the IE/IE-F subset. Further studies are needed to prospectively explore the role of TME subtypes in determining clinical outcomes and IO response.
Research Sponsor: None.

Median overall survival (months) in TME and NLR subsets, with and without IO.

Subset/Treatment	IE/IE-F	F/D	P-value	NLR High	NLR Low	P-value
IO	45.3	15.6	0.14	11.2	22.7	0.04
No IO	14.6	10.8		10.8	57.4	

Identification of differential epigenetic landscapes in subtypes of appendiceal cancer.

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Background: Appendiceal cancers (AC) represent a rare and heterogeneous group of malignancies, often managed with strategies adapted from colorectal cancer (CRC) due to their anatomical proximity. However, marked differences in biological behavior, treatment response, and molecular profiles between AC and CRC necessitate independent study. While genomic data on AC has been explored, epigenetic landscapes remain uncharted. This study establishes the first comprehensive epigenetic profile of appendiceal cancer subtypes, aiming to identify novel biomarkers, therapeutic targets, and prognostic indicators. **Methods:** Tissue specimens from 20 patients with histologically confirmed appendiceal neoplasms and 4 age-matched non-neoplastic controls were analyzed. Malignant subtypes were categorized into three groups: Normal, Low-Grade Appendiceal Mucinous Neoplasms (LAMN, with and without pseudomyxoma peritonei), and Advanced Neoplasia (mucinous adenocarcinoma, non-mucinous adenocarcinoma, and goblet cell adenocarcinoma). Whole-genome methylome profiling was performed using enzymatic methyl-seq for single-base resolution of DNA methylation. Differentially methylated regions (DMRs) were identified with a q-value cutoff of < 0.05 and analyzed using the Whole Genome R package with the methylKit analysis pipeline. **Results:** Epigenetic clustering revealed progressive dysregulation from normal tissue to LAMN and further to advanced neoplasia, supporting a continuum of malignancy. Our preliminary analysis of CpG islands identified 2,621 DMRs between LAMN and normal tissues and 395 DMRs between Advanced Neoplasia and LAMN. In promoter regions, 1,852 DMRs differentiated LAMN from normal, and 283 distinguished Advanced Neoplasia from LAMN. LAMN samples exhibited predominantly hypomethylated regions relative to normal tissues (2,299 vs. 322 for CpG islands; 1,579 vs. 273 for promoters). Conversely, advanced neoplasia demonstrated more hypermethylated regions than LAMN (243 vs. 152 for CpG islands; 195 vs. 88 for promoters). Most DMRs were localized to intronic, distal intergenic, and promoter regions. Key overlapping DMRs included 8 hypomethylated CpG islands, 41 hypermethylated CpG islands, 3 hypomethylated promoters, and 14 hypermethylated promoters. These regions implicate pivotal genes in the progression from LAMN to advanced neoplasia. **Conclusions:** This study pioneers the epigenetic characterization of appendiceal cancers, uncovering unique methylation signatures that differentiate malignant subtypes and normal tissue. Integrating these findings with genomic data highlights critical targets for the detection and molecular classification of appendiceal neoplasms. These insights pave the way for improved diagnostic and therapeutic strategies tailored to this rare malignancy. Research Sponsor: None.

Circulating tumor DNA-based genomic profiling and real-world outcomes in cancer of unknown primary (CUP).

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Background: CUP accounts for <5% of cancers and carries a dismal prognosis with median overall survival of ~13 months. Studies suggest up to one-third of CUP patients (pts) have a potentially targetable alteration (PTA) that may be eligible for molecularly guided therapy (MGT). Liquid biopsy (LB) is a non-invasive method to identify PTAs and genomic clues regarding primary site via circulating tumor DNA (ctDNA). We characterize the ctDNA landscape of PTAs in CUP and evaluate outcomes for pts receiving MGT. **Methods:** Real-world data was sourced via GuardantINFORM, a database aggregating insurance claims and de-identified records of pts with clinical LB via Guardant360. PTAs were defined as alterations with FDA approved therapies in non-CUP indications. Pts with CUP and ≥1 treatment claim after LB were included. Outcomes of pts treated with MGT and pts with the same PTA not treated with MGT were assessed via real-world time to treatment discontinuation (rwTTD), real-world time to next treatment (rwTTNT) and real-world overall survival (rwOS) in months. Log-rank test was used to compare time-to-event outcomes. **Results:** Of 13,324 CUP pts, 50% were male; the median age was 69 years. Majority of pts underwent LB at time of diagnosis (92.1%). In pts with ≥1 genomic alteration identified (91.9%), the most common genomic alterations were *TP53* (55%), *KRAS* (25%), *PIK3CA* (14%), and *EGFR* (12%). A PTA was identified in 29.4% of pts, the most frequent being *PIK3CA* (9.2%), *KRAS* G12C (4.3%), *BRCA1/2* (4%), *ERBB2* (3.9%), *EGFR* (2.8%), *IDH1* (2.5%), *BRAF* V600E (2.4%) and MSI-H (2%). rwTTD was higher for pts with alterations in *EGFR*, *BRAF* V600E, and MSI-H receiving MGT; only *EGFR* reached significance (Table). Similarly, rwTTNT was improved in pts with *EGFR*, *BRAF* V600E alterations and MSI-H, but did not reach significance. rwOS was numerically higher for *BRAF* V600E and *ERBB2* mutated pts receiving MGT (Table). **Conclusions:** This study represents the first large-scale ctDNA genomic profiling of CUP pts with real-world outcomes.LB detected PTAs in 29.4% of CUP pts, similar to tissue-based testing. Our findings support use of LB to identify PTAs in CUP pts; however, prospective trials are needed to assess MGT efficacy. Research Sponsor: None.

Real-world outcomes (in months): MGT vs no MGT.

	rwTTD	rwTTNT	rwOS
EGFR (n=46)	5.8 (95CI: 3-10.27) vs 2.8 (95CI: 2.1-4.5), **p=0.0043**	11.7 (95CI: 6.2-NR) vs 6.5 (95CI: 5.0-NR), p=0.33	12.8 (95CI: 8.9-NR) vs 13.9 (95CI: 7.0-NR), p=0.9
BRAF V600E (n=36)	5.7 (95CI: 4.2-25.1) vs 4.0 (95CI : 3.4-11.4), p=0.48	10.2 (95CI: 6.9-NR) vs 9.1 (95CI: 5.6-NR), p=0.43	35.1 (95CI: 10.2-NR) vs 25.0 (95CI: 7.0-NR), p=0.18
ERBB2 (n=58)	3.9 (95CI: 2.8-5.9) vs 4.2 (95CI: 2.8-6.8), p=0.41	7.0 (95CI: 4.9-NR) vs 6.1 (95CI: 4.2-NR), p=0.96	21.9 (95CI: 11.6-NR) vs 17.0 (95CI: 8.1-NR), p=0.37
MSI-H (n=34)	7.2 (95CI: 4.9-22.5) vs 3.9 (95CI: 2.3-NR), p=0.14	15.4 (95CI: 7.0-NR) vs 10.2 (95CI: 5.5-NR), p=0.77	NR (95CI: 19.0-NR vs 34.5 (95CI: 29.8-NR), p=0.84

TPS4201 Poster Session

A multiregional, randomized, controlled, open-label, phase 3 study of the anti-claudin18.2 (CLDN18.2) antibody-drug conjugate (ADC) arcotatug tavatecan (IBI343) in gastric or gastroesophageal junction adenocarcinoma (G/GEJA): Trial in progress.

Lin Shen, Kohei Shitara, Qi Mei, Changzheng Li, Jia Wei, Xianhe Xie, Ping Chen, Zhihu Li, Ninggang Zhang, Yanqiao Zhang, Lili Sheng, Xiaobing Chen, Qunyi Guo, Jianwei Yang, Zhenyang Liu, Xinjun Liang, Ming Liu, Yongdong Jin, Zhimin Gong, Hui Zhou; Beijing Cancer Hospital, Beijing, China; National Cancer Center Hospital East, Chiba, Japan; Shanxi Bethune Hospital, Taiyuan, China; Shandong Cancer Hospital and Institute, Jinan, China; Nanjing Drum Tower Hospital, Nanjing, China; The First Affiliated Hospital of Fujian Medical University, Fuzhou, China; General Hospital of Ningxia Medical University, Yinchuan, Ningxia, China; Gansu Cancer Provincial Hospital, Lanzhou, Gansu, China; Shanxi Cancer Hospital, Taiyuan, China; Harbin Medical University Cancer Hospital, Harbin, China; The First Affiliated Hospital of Wannan Medical College, Wuhu, China; Henan Cancer Hospital, Zhengzhou, China; Taizhou Hospital of Zhejiang Province, Taizhou, China; Fujian Cancer Hospital, Fuzhou, China; Hunan Cancer Hospital, Changsha, China; Hubei Cancer Hospital, Wuhan, China; West China Hospital of Sichuan University, Chengdu, China; Sichuan Cancer Hospital, Chengdu, China; Xiangyang Central Hospital, Affiliated Hospital of Hubei University of Arts and Science, Xiangyang, China; Innovent Biologics (Suzhou) Co., Ltd., Suzhou, China

Background: CLDN18.2 has been a validated therapeutic target for G/GEJA. As a next-generation ADC, arcotatug tavatecan (IBI343) composed of anti-CLDN18.2 monoclonal antibody conjugated to exatecan (topoisomerase I inhibitor) with unique IgG1 Fc silencing to attenuate antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity. Previous phase 1 studies of IBI343 observed manageable safety profiles with encouraging efficacy in G/GEJA, pancreatic ductal adenocarcinoma and biliary tract cancer (2024 ASCO Annual Meeting [3037], ESMO GI 2024 [396MO], ESMO Asia 2024 [132MO]). Here, we present the trial in progress of a phase 3 study (G-HOPE-001, NCT06238843) evaluating efficacy and safety of IBI343 monotherapy versus treatment of investigator's choice in previously treated patients (pts) with CLDN18.2-positive G/GEJA. **Methods:** This multiregional, randomized, controlled, open-label, phase 3 study planned to enroll 450 pts. Main inclusion criteria are: 1) locally advanced unresectable or metastatic G/GEJA; 2) positive CLDN18.2, defined as immunohistochemical (IHC) membrane staining intensity $\geq$ 2+ in $\geq$ 75% of tumor cells as measured by the VENTANA CLDN18 (43-14A) Assay; 3) radiologically evaluable disease, measurable and/or non-measurable disease per RECIST v1.1; 4) received and progressed on 2-4 prior regimens of systemic therapy which must include a fluoropyrimidine, platinum, and a taxane or irinotecan. Main exclusion criteria are: 1) positive HER-2, defined as IHC 3+ or IHC 2+/ in situ hybridization+; 2) history of treatment with topoisomerase inhibitor-based ADCs. Pts are randomized in a 1:1 ratio to receive IBI343 6mg/kg Q3W in the experimental arm or to receive treatment of investigator's choice including irinotecan, paclitaxel, or trifluridine/tipiracil in the control arm. Stratification factors include region (Asian country/region other than Japan vs. European Union and United States vs. Japan), primary site of the tumor (stomach vs. gastroesophageal junction) and history of prior gastrectomy (yes vs. no). The primary endpoints are progression-free survival (PFS) per RECIST v1.1 and overall survival (OS). The secondary endpoints include objective response rate (ORR), disease control rate (DCR), duration of response (DoR) and time to response (TTR) per RECIST v1.1, quality of life (QoL), safety, pharmacokinetics (PK) and immunogenicity. The trial is currently enrolling pts in China and Japan. Clinical trial information: NCT06238843. Research Sponsor: Innovent Biologics (Suzhou) Co., Ltd.

TPS4202 **Poster Session**

Telisotuzumab adizutecan (ABBV-400; Temab-A) in combination with fluorouracil, leucovorin, and budigalimab in locally advanced/metastatic gastric, gastro-esophageal junction, or esophageal adenocarcinoma (a/m GEA).

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Background: The *MET* proto-oncogene and its receptor tyrosine kinase gene product (c-Met protein) are involved in normal cellular functions such as cell proliferation and differentiation but can be abnormally activated and upregulated in cancer to promote tumor growth. *MET* gene amplification and increased c-Met protein expression are associated with poor survival outcomes in gastric cancer. The antibody-drug conjugate Temab-A (ABBV-400) is composed of the c-Met–directed antibody telisotuzumab conjugated to a potent topoisomerase 1 inhibitor. A phase 1 study (NCT05029882) investigating Temab-A monotherapy demonstrated manageable safety and encouraging efficacy in patients with previously treated, advanced GEA, with an objective response rate of 29% (12/42) and clinical benefit rate of 71% (30/42) (Strickler et al. *Ann Oncol*. 2024;35:1439P). This study evaluates Temab-A in combination with fluorouracil (5-FU), leucovorin/folinic acid (LV), and budigalimab (budi; a PD-1–blocking antibody). **Methods:** This multicenter,phase 2, open-label, randomized study (NCT06628310) will enroll ~180 adult patients with HER2-negative a/m GEA who have not received prior systemic therapy in the a/m setting, have not received a prior PD-(L)1 inhibitor, have Eastern Cooperative Oncology Group performance status 0–1, and have measurable disease per RECIST v1.1. Primary objectives of the study are to evaluate safety and tolerability, evaluate efficacy as measured by progression-free survival and objective response, and select the recommended phase 3 dose of Temab-A in combination with 5-FU, LV, and budi. Secondary objectives include assessment of dose-limiting toxicities (DLTs) in the dose-escalation stage, evaluation of pharmacokinetics, and further evaluation of efficacy measures (duration of response, disease control, and overall survival). The study consists of 2 stages: dose escalation and dose optimization. During BOIN-directed dose escalation, ~18 patients receive escalating doses of Temab-A administered once every 4 weeks (Q4W) in combination with fixed doses of 5-FU (2400 mg/m^2 Q2W), LV (400 mg/m^2 Q2W), and budi (500 mg Q4W). DLTs are assessed during the first 28-day cycle. During dose optimization, ~162 patients are randomized 1:1:1 to 1 of 2 selected doses of Temab-A in combination with 5-FU, LV, and budi or a control arm of FOLFOX + budi. Randomization is stratified by PD-L1 expression and primary tumor location. Treatment is administered until disease progression, intolerable toxicity, or other discontinuation criteria are met. Either archived formalin-fixed paraffin-embedded tissue or a fresh biopsy is required for biomarker research that will include evaluation of c-Met protein expression and *MET* genomic alterations. Clinical trial information: NCT06628310. Research Sponsor: AbbVie, Inc.; n/a.

TPS4203 **Poster Session**

Open-label, single-arm, single-center phase 1b/2 clinical study of fruquintinib combined with trastuzumab and XELOX in the first-line treatment of advanced HER2-positive metastatic gastric or gastroesophageal junction adenocarcinoma.

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Background: Trastuzumab plus chemotherapy has significantly prolonged survival in patients with HER2-positive gastric and gastroesophageal junction (G/GEJ) cancer. The KEYNOTE-811 study suggested that the efficacy of adding pembrolizumab to trastuzumab and chemotherapy was superior to trastuzumab plus chemotherapy. However, only patients with a PD-L1 combined positive score (CPS) of 1 or higher could benefit, while those with PD-L1 CPS < 1 did not benefit from this regimen. Fruquintinib is a highly selective oral tyrosine kinase inhibitor of vascular endothelial growth factor receptors (VEGFRs) 1, 2, and 3. The phase 3 study FRUTIGA demonstrated fruquintinib plus paclitaxel was superior to paclitaxel alone as second-line treatment in patients with G/GEJ cancer. As anti-angiogenesis has a synergistic effect with trastuzumab, we designed this study to evaluate the safety and efficacy of fruquintinib plus trastuzumab, and CAPEOX as first-line treatment for advanced HER2-positive G/GEJ cancer. **Methods:** This is a single-center, single-arm, open-label, phase 1b/2 study. The phase 1b study will adopt a 3+3 design with escalating oral daily dose of 2 to 4 mg (1 mg per level) fruquintinib for days 1-14 in combination with trastuzumab (8mg/kg load, followed by 6mg/kg) intravenously once for day 1, capecitabine 1000mg/m^2 orally twice a day for days 1-14, and oxaliplatin 130mg/m^2 intravenously once for day 1 using a 21-day cycle. The maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of fruquintinib will be determined in the phase 1b study with a dose-limiting toxicity (DLT) period of the first cycle. Major DLTs are defined as any of the following toxicities occurring in the DLT period determined to be related to study treatment: grade ≥ 4 hematological toxicities, grade ≥ 3 non-hematological toxicities, and toxicities that required discontinuation of fruquintinib or trastuzumab ≥ 21 days. 6 to 12 systematic treatment-naïve patients with advanced G/GEJ cancer are expected to be enrolled in the phase 1b study, depending on observed DLTs and the need for dose adjustments. In the phase 2 study, 39 additional patients will be enrolled with RP2D administered. Upon 6-8 cycles of treatment completed, fruquintinib plus trastuzumab and capecitabine will be administered as maintenance treatment. The treatment continues until progressive disease or intolerable toxicity. The primary endpoint of the phase 2 study is PFS. The secondary endpoints include OS, ORR, DCR, DoR, safety, and molecular biomarker exploration. Clinical trial information: ChiCTR2300074767. Research Sponsor: None.

TPS4204 Poster Session

ARTEMIDE-Gastric01: A phase 3 randomized study of rilvegostomig with fluoropyrimidine and trastuzumab deruxtecan (T-DXd) as first-line (1L) treatment for locally advanced or metastatic HER2-positive gastric or gastroesophageal junction cancer (GC/GEJC).

Rui-Hua Xu, Diogo Bugano Diniz Gomes, Jen-Shi Chen, Florian Lordick, Andrew Scott Paulson, Sun Young Rha, Josep Tabernero, Kensei Yamaguchi, Jun Zhang, Jacqui Aitchison, Zhuoer Sun, Qian Zhu, Ye Xia, Anastasia Jiang, Xia Li, Osama E. Rahma, Manish A. Shah; Department of Medical Oncology, Sun Yat-Sen University Cancer Center, State Key Laboratory of Oncology in South China, Guangdong Provincial Clinical Research Center for Cancer, Sun Yat-Sen University, Guangzhou, China; Hospital Israelita Albert Einstein, São Paulo, Brazil; Hospital Municipal Vila Santa Catarina, São Paulo, Brazil; Department of Hematology and Oncology, Linkou Chang-Gung Memorial Hospital and Chang-Gung University, Tao-Yuan City, Taiwan; Department of Medicine and University Cancer Center Leipzig, University of Leipzig Medical Center, Leipzig, Germany; Texas Oncology-Baylor Charles A. Sammons Cancer Center, Dallas, TX; Department of Internal Medicine, Yonsei Cancer Center, Yonsei University Health System, Seoul, South Korea; Medical Oncology Department, Vall d'Hebron Hospital Campus & Institute of Oncology (VHIO), IOB-Quiron, UVic-UCC, Barcelona, Spain; The Cancer Institute Hospital of JFCR, Tokyo, Japan; Department of Oncology, Rui Jin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; Global Clinical Operations, AstraZeneca, Macclesfield, United Kingdom; AstraZeneca, Shanghai, China; Oncology R&D, AstraZeneca, Shanghai, China; Statistics, AstraZeneca, Gaithersburg, MD; Global Oncology R&D, AstraZeneca, Waltham, MA; Weill Cornell Medical College, New York, NY

Background: Patients with GC/GEJC often present with advanced disease, and prognosis for these patients is poor, with a 5-year relative survival rate of ~5%, highlighting a need for new treatment options. HER2 overexpression/amplification occurs in ~20% of cases. Adding immune checkpoint inhibition to trastuzumab (anti-HER2 monoclonal antibody) and chemotherapy has shown clinical benefit in patients with advanced HER2-positive GC/GEJC (Janjigian YY, et al. *N Engl J Med* 2024), and led to the approval of pembrolizumab (programmed cell death-1 [PD-1] inhibitor), trastuzumab, and chemotherapy for HER2-positive GC/GEJC with programmed cell death ligand-1 combined positive score (PD-L1 CPS) ≥1. T-DXd (a HER2-directed antibody-drug conjugate) is approved for the treatment of patients with locally advanced/metastatic HER2-positive GC/GEJC who have received a prior trastuzumab-based regimen. In addition, dual inhibition of PD-1 or PD-L1 and the immune checkpoint T cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain (TIGIT) has shown encouraging results across multiple tumor types, without major increases in high-grade toxicity compared with PD-1 or PD-L1 inhibition alone. Rilvegostomig is a monovalent, bispecific, humanized IgG1 monoclonal antibody targeting both PD-1 and TIGIT receptors that has shown encouraging efficacy with manageable safety as monotherapy in non-small-cell lung cancer (Hiltermann TJN, et al. WCLC 2024. Oral presentation 1751) and with chemotherapy in HER2-negative GC/GEJC (Herrero FR, et al. *Ann Oncol* 2024. Abs 1422P). **Methods:** ARTEMIDE-Gastric01 (NCT06764875) is a phase 3, randomized, open-label, sponsor-blinded, multicenter, global study that will assess the efficacy and safety of rilvegostomig with T-DXd and chemotherapy as 1L treatment in HER2-positive GC/GEJC with PD-L1 CPS ≥1. Approximately 840 participants (pts) will be randomized to Arm A: rilvegostomig + T-DXd + investigator's (INV) choice of capecitabine or 5-fluorouracil (5-FU); Arm B: pembrolizumab + trastuzumab + INV choice of 5-FU and cisplatin (FP) or capecitabine and oxaliplatin (CAPOX); Arm C: rilvegostomig + trastuzumab + INV choice of FP or CAPOX. Eligible pts will have previously untreated, unresectable, histologically confirmed, locally advanced/metastatic HER2-positive and PD-L1 CPS ≥1 GC/GEJC and an ECOG performance status of 0 or 1. Dual-primary endpoints are progression-free survival (RECIST v1.1; blinded independent central review) and overall survival in all randomized pts. Secondary endpoints include safety/tolerability, objective response rate, and duration of response. Enrollment is planned across ~25 countries in Asia, Australia, Europe, and North and South America. Clinical trial information: NCT06764875. Research Sponsor: AstraZeneca.

TPS4205 **Poster Session**

A randomized controlled trial comparing conversion surgery with palliative chemotherapy in patients with initially unresectable cStage IVB/pStage IV advanced gastric cancer who presented remarkable response to chemotherapy: JCOG2301 (Conversion study).

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Background: Conversion surgery is a surgical treatment for patients with initially unresectable cStage IVB gastric cancer who presented remarkable response to palliative chemotherapy aiming at n R0 resection expecting long survival including he disease. This study is a randomized controlled phase III trial aimed to evaluate the efficacy of conversion surgery comparing to palliative chemotherapy. **Methods:** Eligibility criteria include the followings : (1) Histologically proven adenocarcinoma of the stomach. (2) Diagnosed as clinical stage IVB or pathological stage IV according to the Japanese Classification of Gastric Carcinoma (15th edition), with at least one of the following unresectable distant metastases before chemotherapy. (i) Four or more liver metastases. (ii) Distant lymph node metastasis beyond para-aortic lymph node No.16a2/16b1. (iii) Peritoneal dissemination diagnosed with imaging examination or P1b/P1c peritoneal dissemination diagnosed with laparotomy or laparoscopy. (3) Undergoing first-line chemotherapy regardless of nivolumab or trastuzumab use. (4) Confirmation of no peritoneal metastasis or localization at a limited area close to the stomach by laparoscopy or laparotomy after initiation of chemotherapy, with CY0 status in peritoneal lavage cytology. (5) Response to chemotherapy of distant metastasis diagnosed before initiating first-line chemotherapy that meets the following (i) and (ii) before registration. (i) Liver metastasis: three or fewer liver metastasis. (ii) Distant lymph node metastasis excluding No.16a2/16b1: disappearance or reduction to a long axis of less than 6 mm. The primary endpoint is overall survival. After confirming eligibility, patients are registered and randomized (1:1) to either the palliative chemotherapy alone arm or the conversion surgery arm. We assumed the median survival timeis 19 months after registration for the chemotherapy alone arm additional efficacy for overall survival in the conversion surgery arm corresponding to a hazard ratio of 0.7. This study requires 126 patients to observe 102 deaths, with power of 70% and a one-sided alpha of 10%, considering the rarity of patients with stage IV gastric cancer who exhibit a significant response to palliative chemotherapy, an accrual period of 5 years, and a follow-up period of 3 years. This trial was initiated in September 2024, and the first patient was enrolled in January 2025. Clinical trial information: jRCTs031240340. Research Sponsor: Japan Agency for Medical Research and Development (AMED).

TPS4206 Poster Session

A randomized, double-blinded, international phase III trial comparing HLX22 in combination with trastuzumab and chemotherapy versus trastuzumab and chemotherapy with or without pembrolizumab for first-line treatment for HER2-positive locally advanced or metastatic G/GEJ cancer.

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Background: Combination therapy with trastuzumab and chemotherapy is the first-line systemic treatment for human epidermal growth factor receptor 2 (HER2) positive advanced gastric or gastroesophageal junction (G/GEJ) cancer. Among patients whose tumors express programmed death ligand 1 (PD-L1; defined as combined positive score [CPS] ≥ 1), treatment options also include pembrolizumab plus trastuzumab and chemotherapy. Survival outcomes remain unsatisfactory despite these advances. HLX22 is an anti-HER2 antibody that targets a different epitope than trastuzumab. HLX22 has shown improved progression-free survival (PFS) when added to trastuzumab plus oxaliplatin and capecitabine (XELOX) in a phase 2 study (NCT04908813). Here we present the design of a phase III randomized controlled study. **Methods:** This randomized, double-blind, two-arm phase III clinical study aims to compare the efficacy and safety of HLX22 in combination with trastuzumab and XELOX versus (vs) trastuzumab and XELOX with or without ($\pm$) pembrolizumab in patients with HER2-positive, advanced G/GEJ cancer and no prior antitumor therapy in the advanced setting. Key inclusion criteria include histologically or cytologically confirmed diagnosis of previously untreated, locally advanced unresectable or metastatic HER2-positive G/GEJ adenocarcinoma. Key exclusion criteria include prior use of any HER2-target therapy. Approximately 550 eligible patients will be enrolled from multiple regions across the globe and randomly assigned in a 1:1 ratio to receive HLX22 (15 mg/kg) + trastuzumab + XELOX $\pm$ placebo (for pembrolizumab) or placebo (for HLX22) + trastuzumab + XELOX $\pm$ pembrolizumab. HLX22 will be administered intravenously on Day 1 of each 21-day treatment cycle until loss of clinical benefit, death, intolerable toxicity, withdrawal of informed consent, or other reasons. The stratification factors include HER2 immunohistochemistry (3+ vs 2+), geographic region (Asia vs Europe/North America vs rest of the world), primary tumor site (gastric vs gastroesophageal junction), and tumor PD-L1 expression (CPS < 1 or not evaluable vs $1 \leq$ CPS < 10 vs CPS ≥ 10). The dual primary endpoints are PFS assessed by independent radiology review committee per RECIST v1.1 and overall survival. Secondary endpoints include investigator-assessed PFS, objective response rate, PFS on the subsequent line of therapy, duration of response, safety, pharmacokinetics, immunogenicity, and quality of life. This study is currently open for enrollment and has completed first dose of the first patient. Clinical trial information: NCT06532006. Research Sponsor: Shanghai Henlius Biotech, Inc.

TPS4207 Poster Session

An open-label, randomized, multicenter, phase 3 study of trastuzumab deruxtecan (T-DXd) + chemotherapy (chemo) ± pembrolizumab (pembro) versus chemo + trastuzumab ± pembro in first-line metastatic HER2+ gastric or gastroesophageal junction (GEJ) cancer: DESTINY-Gastric05.

Kohei Shitara, Lin Shen, Jeeyun Lee, Paulo Marcelo Hoff, Elizabeth Catherine Smyth, Daniel Barrios, Kojiro Kobayashi, Yasuyuki Okuda, Takahiro Kamio, Yelena Y. Janjigian; National Cancer Center Hospital East, Chiba, Japan; State Key Laboratory of Holistic Integrative Management of Gastrointestinal Cancers, Department of GI Oncology, Peking University Cancer Hospital & Institute, Beijing, China; Samsung Medical Center, Seoul, South Korea; University of São Paulo, Sao Paulo, Brazil; Oxford University Hospitals NIHR Biomedical Research Centre, Churchill Hospital, Oxford, United Kingdom; Daiichi Sankyo, Inc., Basking Ridge, NJ; Daiichi Sankyo Co., Ltd., Tokyo, Japan; Gastrointestinal Oncology Service, Memorial Sloan Kettering Cancer Center, New York, NY

Background: An unmet medical need remains in patients (pts) with HER2+ gastric or GEJ cancer. HER2 is a validated target in up to 20% of pts with gastric or GEJ cancer. The KEYNOTE-811 trial demonstrated that adding pembro to trastuzumab and chemo improved progression-free survival (PFS) and overall survival (OS) versus placebo for first-line treatment of pts with HER2+ gastric or GEJ cancer with a PD-L1 combined positive score (CPS) ≥1 (Janjigian Y et al. *N Engl J Med.* 391;1360:2024). In the DESTINY-Gastric03 trial, first-line combinations involving T-DXd, a HER2-directed antibody-drug conjugate, and fluoropyrimidine (5-FU or capecitabine [CAPE]) ± pembro showed acceptable safety and encouraging efficacy in pts with HER2+ gastric or GEJ cancer, including pts with CPS < 1 (Janjigian Y et al. *Ann Oncol.* 35;S878:2024). Building on this evidence, the phase 3 DESTINY-Gastric05 trial aims to bring a potentially improved platinum-free treatment approach for all pts with HER2+ gastric or GEJ cancer. **Methods:** DESTINY-Gastric05 (NCT06731478) is an open-label, randomized, multicenter, phase 3 global trial designed to evaluate the efficacy and safety of T-DXd in combination with 5-FU (or CAPE) + pembro versus standard-of-care chemo with trastuzumab + pembro as first-line treatment in pts with unresectable, locally advanced or metastatic centrally confirmed HER2+ (immunohistochemistry [IHC] 3+ or IHC 2+/in situ hybridization+) gastric or GEJ cancer with a CPS ≥1. Pts must have ≥1 RECIST v1.1 measurable lesion, a left ventricular ejection fraction ≥50%, and an Eastern Cooperative Oncology Group performance status of 0 or 1. Approximately 576 pts will be randomly assigned in a 1:1 ratio to receive: T-DXd 5.4 mg/kg + either 5-FU or CAPE + pembro (arm M1); or trastuzumab + platinum-based chemo (either cisplatin + 5-FU or oxaliplatin + CAPE) + pembro (arm M2). The primary efficacy endpoint is PFS based on blinded independent central review (BICR), and the key secondary endpoint is OS. Other secondary endpoints include overall response rate, duration of response, and time to response per RECIST v1.1 assessed by BICR and investigator. Safety and tolerability will also be assessed. An exploratory cohort (approximately 150 pts) will evaluate the efficacy and safety of T-DXd in combination with 5-FU or CAPE versus trastuzumab plus standard-of-care chemo in pts with PD-L1 CPS < 1. Clinical trial information: NCT06731478. Research Sponsor: Daiichi Sankyo, Inc.

TPS4208 **Poster Session**

A phase II study of sacituzumab govitecan for advanced esophageal squamous cell carcinoma patients (SG-ESCC).

Jhe-Cyuan Guo, Tsung-Che Wu, Ta-Chen Huang, Hung-Yang Kuo, Chien-Huai Chuang, Wei-Chen Lu, Chia-Chi Lin, Chih-Hung Hsu; National Taiwan University Cancer Center, Taipei, Taiwan; National Taiwan University Hospital Hsin-Chu Branch, Hsinchu, Taiwan; National Taiwan University Hospital, Taipei, Taiwan; National Taiwan University Hospital, Taipei City, Taiwan; Department of Oncology, National Taiwan University Hospital Yunlin Branch, Yunlin, Taiwan

Background: Esophageal squamous cell carcinoma (ESCC) remains a significant global health challenge, particularly in Asia. There are limited treatment options for advanced ESCC patients who fail platinum-based chemotherapy and anti-PD-1/PD-L1 therapy, resulting in poor prognoses. Trophoblast cell surface antigen 2 (Trop-2), a transmembrane protein overexpressed in ESCC, offers a potential therapeutic target due to its differential expression between tumors and normal tissues. Sacituzumab govitecan, an antibody-drug conjugate (ADC) comprising an anti-Trop-2 antibody linked to a topoisomerase I inhibitor payload, has shown efficacy in triple-negative and hormone receptor-positive breast cancers. This study aims to investigate the efficacy and safety of sacituzumab govitecan in patients with advanced ESCC.
Methods: This investigator-initiated, prospective, phase II, single-arm, multi-center trial evaluates the efficacy and safety of sacituzumab govitecan (10 mg/kg IV on days 1 and 8 of a 21-day cycle) in advanced ESCC patients. Eligible patients must have failed prior platinum-based chemotherapy and anti-PD-1/PD-L1 therapy, exhibit measurable disease per RECIST 1.1, and have an ECOG performance status ≤1. The primary endpoint is the objective response rate (ORR) by RECIST 1.1. Secondary endpoints include overall survival, progression-free survival, duration of response, and safety outcomes. Biomarker analyses will explore Trop-2 expression and other molecular markers associated with treatment efficacy and resistance as well as toxicity. A total of 35 patients will be enrolled employing Simon's two-stage design, with a type I error rate of 0.1 and 80% power to detect an ORR ≥25%, considered promising compared to the historical control of ≤10%. In the first stage, 16 patients will be accrued, with ≥2 responses required to proceed to the second stage of 15 additional patients. Accounting for an anticipated 10% dropout rate, the study aims to complete enrollment within 24 months. Enrollment began in August 2024, and as of December 2024, 5 of the planned 35 patients have been enrolled. Clinical trial information: NCT06329869. Research Sponsor: Gilead Sciences.

TPS4209 Poster Session

KEYMAKER-U06 substudy 06E: A phase 1/2 open-label, umbrella platform study of ifinatamab deruxtecan in combination with pembrolizumab with or without chemotherapy for first-line treatment of advanced esophageal squamous cell carcinoma (ESCC).

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Background: There is a substantial need for more effective and tolerable first-line treatment options for patients with advanced ESCC. B7-H3 is a type 1 transmembrane protein that is highly expressed in several cancers, including ESCC, and is associated with a poor prognosis. Ifinatamab deruxtecan (I-DXd; formerly DS-7300a/MK-2400) is a B7-H3–directed antibody-drug conjugate comprising a humanized anti–B7-H3 IgG1 monoclonal antibody (ifinatamab) covalently linked to a potent topoisomerase I inhibitor payload (DXd; an exatecan derivative) by a cleavable linker. In the phase 1/2 DS7300-A-J101 study, I-DXd monotherapy showed promising antitumor activity in participants (pts) with advanced ESCC. KEYMAKER-U06 is an open-label, phase 1/2, umbrella platform study designed to evaluate investigational agents with or without pembrolizumab and/or chemotherapy for advanced gastroesophageal cancer. Substudy 06E (NCT06780111) will be conducted to evaluate I-DXd plus pembrolizumab with or without chemotherapy as first-line therapy for advanced ESCC. **Methods:** Eligible pts are aged ≥18 years with previously untreated, histologically or cytologically confirmed, locally advanced unresectable or metastatic ESCC, measurable disease per RECIST v1.1 by investigator review and verified by blinded independent central review (BICR), and an Eastern Cooperative Oncology Group performance status of 0 or 1. Pts will be assigned to 1 of 4 treatment arms: arm 1 (reference treatment; pembrolizumab 200 mg IV Q3W for ≤35 cycles plus chemotherapy [mFOLFOX6: oxaliplatin 85 mg/m^2 IV Q2W plus 5-FU 400 mg/m^2 (bolus) and 2400 mg/m^2 (continuous) IV Q2W plus leucovorin 400 mg/m^2 IV Q2W]); arm 2 (I-DXd 12 mg/kg IV Q3W plus pembrolizumab); arm 3 (I-DXd 12 mg/kg plus pembrolizumab plus 5-FU 400 mg/m^2 [bolus] and 2400 mg/m^2 [continuous] IV Q2W plus leucovorin 400 mg/m^2 IV Q2W); and arm 4 (I-DXd [8 mg/kg or 12 mg/kg] IV plus pembrolizumab plus 5-FU 2400 mg/m^2 IV and oxaliplatin 60 mg/m^2). Approximately 209 pts will be enrolled. A safety lead-in phase with ≤29 pts will be conducted in arms 2 (n ≤6), 3 (n ≤10), and 4 (n ≤13) using a Bayesian optimal interval design to confirm the safety and recommended phase 2 dose (RP2D; arm 4 only) of I-DXd in combination with other agents; this phase will be conducted sequentially, starting with arm 2, followed by arms 3 and 4. Thereafter, ≤180 pts will be included in the randomized phase (≤60 in arm 1; ≤40 each in arms 2-4). Pts will be randomly assigned 1:2 to arm 1 and the investigational arms. Primary outcomes are safety and tolerability, RP2D of I-DXd, and objective response rate per RECIST v1.1 by BICR for the selected dose. Secondary outcomes include DOR and PFS per RECIST v1.1 by BICR, OS, and pharmacokinetics of I-DXd in combination with other agents. Enrollment is ongoing. Clinical trial information: NCT06780111. Research Sponsor: Daiichi Sankyo Company, Limited and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

TPS4210 **Poster Session**

A phase II study of perioperative intraperitoneal paclitaxel in patients with gastric adenocarcinoma and carcinomatosis or positive cytology.

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Background: Over the last 2 decades, intraperitoneal chemotherapy has been found to have activity for select subgroups of patients with carcinomatosis from colon, ovarian, appendiceal, and recently, gastric origins. However, there is little data to support an aggressive surgical approach of cytoreduction (debulking) and intraperitoneal therapy for patients with gastric cancer and positive cytology or carcinomatosis. Recently, the DRAGON-01 randomized trial reported improvement in outcomes for the addition of intraperitoneal paclitaxel as part of a bidirectional approach with systemic paclitaxel and S-1 for patients with gastric cancer and peritoneal metastases. However, there are few studies supporting intraperitoneal paclitaxel in Western populations. As systemic therapy is improving with concomitant targeted and immunotherapy, intraperitoneal therapy may be best utilized in Western populations after standard of care systemic therapy. Therefore, the purpose of this clinical trial is to determine the efficacy and safety of perioperative intraperitoneal paclitaxel in patients with stage IV gastric cancer limited to the peritoneum after treatment with systemic chemotherapy. **Methods:** Patients with gastric and gastroesophageal adenocarcinoma and positive peritoneal cytology or carcinomatosis that have completed treatment with systemic chemotherapy are offered participation in the study. Patients with metastatic disease not limited to the peritoneum are excluded. Type and duration of systemic chemotherapy is left to the discretion of the treating medical oncologist. Immunotherapy or Her2-directed therapy may continue during the trial. We have recently completed a Phase I clinical trial demonstrating doses of up to 100 mg/m^2 were safe (NCT04220827; PMID: 39287936). Therefore, 100 mg/m^2 is administered intraperitoneal every 2 weeks for three treatments before and after gastrectomy. We also modified the trial to allow for the inclusion of heated intraperitoneal chemotherapy during gastrectomy. The primary outcome is overall survival from the date of diagnosis of stage IV disease, with secondary outcomes of safety. After completion of study–related treatment, subjects will be followed until recurrence and/or death for up to three years. Sixteen of planned 30 patients have been enrolled (NCT05977998). Clinical trial information: NCT05977998. Research Sponsor: None.

TPS4212 **Poster Session**

Repurposing itraconazole for secondary prevention of metaplasia and primary prevention of cancer in patients with high-risk Barrett's esophagus in combination with ablation.

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Background: To prevent invasive esophageal adenocarcinoma (EAC), endoscopic eradication therapy (EET) is used to remove its precursor, Barrett's esophagus (BE) with dysplasia. EET combines endoscopic removal of visible lesions with radiofrequency ablation (RFA) of surrounding BE to achieve complete remission of intestinal metaplasia (CRIM) and complete eradication of dysplasia (CED) to halt progression to cancer. Unfortunately, EET has metaplasia recurrence rates of 12.4%/year; thus, adjunctive cancer interception agents are needed to maintain the gains of EET. Data from pre-clinical studies and patient tissues demonstrate that the Hedgehog (Hh) pathway regulates esophageal stem cell activity and cell fate determination (squamous versus intestinal). Post-RFA reactivation of Hh signaling is hypothesized to drive BE recurrence; however, current FDA-approved Hh inhibitors are expensive and toxic. The antifungal itraconazole inhibits Hh signaling and has demonstrated antitumor activity in multiple cancers. In addition, it inhibits VEGFR and PI3K-AKT pathways, which are critical to BE development and neoplastic progression. Given its safety and affordability, itraconazole represents a promising strategy to reduce BE recurrence and EAC risk. **Methods:** This randomized, phase 2b, double-blind, placebo-controlled trial will evaluate itraconazole's efficacy in accelerating BE eradication. Participants with high-risk BE, defined as BE $\geq$2 cm with low/high-grade dysplasia or intramucosal/T1 adenocarcinoma, undergoing ablation will be enrolled. Participants will be randomized 1:1 to receive 300 mg of oral itraconazole or placebo for two weeks before and four weeks after their first 2 sessions of EET. The primary endpoint is time to CRIM, a surrogate for long-term BE recurrence, measured in days. Secondary endpoints include time to CED, 12-month BE recurrence rates, safety, tolerability, and correlations between itraconazole levels and patient-reported outcomes. We will enroll 74 patients (37 per arm). We shall use a two-sided log rank test for right-censored time to event analysis to assess differences. The sample size calculation is based on anticipated surviving proportions at specific study times. We assume that the surviving non-CRIM proportions of patients at 3, 6, 9, and 12 months in the control arm to be 0.8, 0.5, 0.2, 0.1, respectively, and in the treatment arm to be 0.5, 0.2, 0.1, 0.05, respectively. To detect this effect size with 80% power at 5% level of significance, we need 30 evaluable participants in each group (with a plan to enroll 37 per arm to account for attrition). A Cox model will adjust for demographic and clinical variables. If successful, this trial could establish itraconazole as a novel adjunct to EET, reducing BE recurrence and lowering EAC risk. Clinical trial information: NCT06732388. Research Sponsor: National Cancer Institute; UG1-CA242632.

TPS4213 Poster Session

Total neoadjuvant therapy with induction immunochemotherapy and chemo-radiotherapy followed by surgery for locally advanced esophageal squamous cell carcinoma (TNT-ESCC).

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Background: Locally advanced esophageal squamous cell carcinoma (ESCC) is indicated for multi-modalities treatment strategies, including a neoadjuvant chemoradiotherapy (CRT) followed by surgery. While the CROSS trial established neoadjuvant CRT as a standard of care, distant metastasis remains a significant cause of treatment failure. Immune checkpoint inhibitors (ICIs) have demonstrated survival benefits in advanced or metastatic ESCC, and adjuvant nivolumab has shown efficacy following neoadjuvant CRT in locally advanced ESCC. Integrating ICI earlier in the treatment sequence through total neoadjuvant therapy may enhance the immune response against the primary tumor and the hidden metastases and potentially lead to improved survival outcomes. This phase II study evaluates induction immunochemotherapy followed by CRT before surgery in locally advanced ESCC. **Methods:** This is a single-center, single-arm, phase II study enrolling 50 patients with histologically confirmed ESCC (T3/4aN0M0 or T1-4aN1-3M0 according to the AJCC Cancer Staging System 8th ed). Eligible patients must have primary intrathoracic esophageal tumor ≤10 cm in length and ≤5 cm in radial diameter, an ECOG performance status of 0-1, and adequate organ function. Patients will receive induction immunochemotherapy consisting of tislelizumab (200 mg every 3 weeks), paclitaxel (175 mg/m^2 every 3 weeks), and cisplatin (75 mg/m^2 every 3 weeks) for two cycles. This is followed by CRT consisting of radiotherapy (45 Gy in 25 fractions, 1.8 Gy/day, 5 days/week) plus chemotherapy with weekly paclitaxel (50 mg/m^2) and cisplatin (30 mg/m^2) for 5 weeks. Esophagectomy will be performed 6 to 8 weeks after completing CRT. The primary endpoint is pathologic complete response (pCR) rate, defined as no residual tumor in the resected primary site and lymph nodes. We hypothesize that the pCR rate will increase from 35% (the historical control) to 55%. Based on a binomial precision design, the study is of 80% power and a unilateral α error of 0.05 to detect a statistically significant difference in pCR rate. Secondary endpoints include major pathological response rate, R0 resection rate, disease-free survival, event-free survival, distant metastasis-free survival, overall survival and safety. The study starts patient enrollment in March 2025 (registered at ClinicalTrials.gov as NCT06764355). Clinical trial information: NCT06764355. Research Sponsor: National Taiwan University Hospital; BeiGene.

TPS4214 Poster Session

PROSPERO: A phase 3 randomized, placebo (Pbo)-controlled study of amezalpat (TPST-1120), a peroxisome proliferator-activated receptor a (PPARα) inhibitor, in combination with atezolizumab + bevacizumab (AB) for patients (pts) with unresectable or metastatic hepatocellular carcinoma (mHCC) not previously treated with systemic therapy.

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Background: PPARα is a fatty acid ligand-activated transcription factor that regulates genes involved in fatty acid oxidation (FAO), angiogenesis, and inflammation. In HCC and other tumor types, PPARα signaling promotes tumor growth and also modulates the tumor immune microenvironment to suppress antitumor immunity. Amezalpat (TPST-1120) is an investigational PPARα antagonist that inhibits FAO, targeting the bioenergetic requirements of cancer cells and restoring anticancer immune pathways. HCC has the highest PPARα expression of any major tumor type. In preclinical studies of HCC, including ß-catenin activated disease, amezalpat exhibits anti-cancer activity as a single agent and demonstrates complementary efficacy in combination with PD-L1 and VEGF inhibitors. In an ongoing global randomized Phase 1b/2 study in pts with unresectable or mHCC not previously treated with systemic therapy, amezalpat in combination with atezolizumab + bevacizumab (TPST-AB) was tolerable and was associated with a clinically meaningful improvement in multiple efficacy endpoints, including overall survival (OS) and confirmed objective response rate (ORR), compared to AB alone. Here we describe a follow-up pivotal Phase 3 study to evaluate the safety and efficacy of TPST-AB vs Pbo plus AB (Pbo-AB) in pts with unresectable or mHCC (NCT06680258). **Methods:** This Phase 3, global, randomized, double-blind study will enroll ~740 pts with unresectable or mHCC. Key eligibility criteria include no prior systemic therapy (prior locoregional therapy allowed), ECOG PS 0-1, Child-Pugh Class A, and measurable disease by RECIST v1.1; pts with fibrolamellar/sarcomatoid HCC, mixed cholangiocarcinoma/HCC, and untreated active HBV are not eligible. Pts will be randomized 1:1 to receive oral amezalpat 600 mg or Pbo twice daily along with the approved doses of atezolizumab and bevacizumab every 3 weeks, until unacceptable toxicity or loss of clinical benefit. Randomization will be stratified by geographic region (Asia excluding Japan vs rest of world), macrovascular invasion and/or extrahepatic spread (y/n), baseline α-fetoprotein ($<$ 400 vs $\geq$400 ng/mL), and baseline ECOG PS (0 vs 1). The primary efficacy endpoint is OS. Key secondary efficacy endpoints include progression-free survival and ORR (RECIST v1.1). Exploratory analyses will include outcome by PD-L1 expression and ß-catenin mutational status. Interim analyses for futility (30% OS events) and efficacy (70% OS events) are planned. Findings of this pivotal study will inform the efficacy and safety profile of amezalpat added to AB vs AB alone in pts with unresectable or mHCC not previously treated with systemic therapy. Clinical trial information: NCT06680258. Research Sponsor: Tempest Therapeutics, Inc.

TPS4215 **Poster Session**

RHEA-1: First-in-human (FIH) study of AZD9793, a first-in-class CD8-guided T cell-engager (TCE) for glypican-3-positive (GPC3+) advanced or metastatic hepatocellular carcinoma (HCC).

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Background: GPC3 is an oncofetal protein expressed in 70–80% of HCC and is associated with poor prognosis. Preliminary clinical research on GPC3-specific CAR-T treatment has validated GPC3 as a therapeutic target in HCC. Its expression is largely confined to the surface of tumor cells, making it an ideal target for TCEs. AZD9793, a trispecific IgG1 monoclonal antibody, is a first-in-class CD8-targeted TCE that directly engages tumor-infiltrating T cells and GPC3+ tumors, forming a bridge that activates T cells leading to tumor cell lysis and T cell proliferation. AZD9793 promotes potent GPC3+ HCC cell killing through preferential engagement of CD8+ T cells, while minimizing CD4+ T cell activation and unwanted cytokine release. The novel mechanism of action combines bivalent GPC3 binding, CD8-biased engagement, and low-affinity T cell receptor binding to improve cytotoxicity and reduce the risk of cytokine release syndrome compared with other TCEs. **Methods:** RHEA-1 is the FIH trial of AZD9793 monotherapy. Eligible patients in this modular, Phase I/II, open-label, multicenter study are adults (≥18 years old) with prospective centrally determined GPC3+ advanced or metastatic HCC with ≥1 measurable lesion by RECIST v1.1, who have received ≥1 line of prior systemic treatment and have an ECOG performance status of 0 or 1. Patients with hepatitis B are eligible if they receive antiviral treatment to ensure adequate viral suppression before enrollment and for ≥6 months after the study; and with hepatitis C if they are being managed per local practice. The study includes Module 1 (intravenous AZD9793) and Module 2 (subcutaneous AZD9793), each comprising dose escalation (Part A) and dose expansion (Part B). Module 1 Part A1 (fixed dose) will start with an accelerated titration design and will then switch to a modified toxicity probability interval-2 algorithm after the first 4 dose cohorts or earlier if dose-limiting toxicities (DLTs) are reported. Part A2 (step-up dosing) may open in either Module based on emerging safety data from Part A1. Part B may be initiated in one or both Modules. Primary endpoints include safety and tolerability in terms of DLTs (only in dose escalation) and adverse events to establish maximum tolerated dose, optimal biological dose, and recommended phase II dose; and objective response rate (only in dose expansion) by investigator assessment (IA) per RECIST v1.1. Secondary endpoints include preliminary efficacy (only in dose escalation) in terms of response and progression-free survival by IA, as well as overall survival (only in dose expansion), pharmacokinetics, immunogenicity, and CD8+ T cell infiltration pre- and post-treatment. No formal statistical hypothesis is proposed; all variables will be reported descriptively. The study (NCT06795022) is currently enrolling in the US and APAC. Clinical trial information: NCT06795022. Research Sponsor: AstraZeneca.

TPS4216 **Poster Session**

Phase II trial of zanzalintinib (XL-092) in combination with durvalumab and tremelimumab in unresectable hepatocellular carcinoma (ZENOBIA).

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Background: Despite the evolving novel treatment options, the prognosis for advanced hepatocellular carcinoma (HCC) remains poor, with a 4-year survival rate of approximately 25%. Immune checkpoint inhibitors (ICIs), including the combination of durvalumab (Durva) & tremelimumab (Treme), represents the current standard-of-care for frontline HCC treatment. However, therapy resistance, either primary or secondary, often arises due to the immunosuppressive tumor microenvironment (TME). VEGFR is a well-established therapeutic target in HCC. Cabozantinib (Cabo), a multi-target tyrosine kinase inhibitor (TKI), is approved for later-line use per the CELESTIAL trial, and it also demonstrated significant TME modulation through antiangiogenic effects. A Phase II study (CHECKMATE 040) reported an impressive objective response rate (ORR) of 29% with the combination of ipilimumab/nivolumab and Cabo but noted high toxicity rates. Zanzalintinib (Zanza) is a novel TKI targeting VEGFR, MET, & TAM kinases (TYRO3, AXL, MER), key mediators of angiogenesis, tumor growth, metastasis, and TME immunosuppression. With a target profile similar to Cabo but an improved pharmacokinetic profile & a shorter half-life (16–22 hours), Zanza has demonstrated potential synergy with ICIs in preclinical and early-phase trials, suggesting enhanced sensitivity by fostering an immune-permissive TME. This phase II study evaluates the safety & efficacy of Zanza combined with Durva and Treme in HCC. **Methods:** This open-label, non-randomized Phase II trial consists of two parallel cohorts. Eligible patients must have unresectable HCC, be treatment-naïve in the unresectable setting, & have ECOG performance status of 0-1. Exclusion criteria include Child-Pugh score >7, known autoimmune diseases, heightened risk of gastrointestinal perforation or fistula formation, and known gastric or esophageal varices. The study begins with a safety lead-in phase of 9–12 patients to establish the recommended Phase II dose. The two cohorts aim to explore the optimal sequential strategy for combining Zanza with Durva & Treme. Cohort A: Zanza is administered during Cycle 1, followed by Durva + Treme in Cycle 2. Cohort B: Durva + Treme is administered during Cycle 1, followed by Zanza and Durva in Cycle 2. Both cohorts will continue with Zanza and Durva in subsequent cycles. A total of 40 participants (20 per cohort) will be enrolled. The primary endpoint is the ORR assessed by imRECIST 1.1. Secondary endpoints include the conversion rate to resectable or transplant-eligible disease, disease control rate, median PFS and OS, and landmark PFS & OS at 6, 12, 24, and 36 months. Safety and tolerability will also be evaluated. Comprehensive translational analyses include bulk RNA sequencing, spatial transcriptomics of baseline tumor biopsies, & serial ctDNA monitoring. Trial enrollment commenced in December 2024. Clinical trial information: NCT06698250. Research Sponsor: Exelixis.

TPS4217 Poster Session

A randomized phase 2 study of casdozokitug, an IL-27 targeting antibody, in combination with toripalimab plus bevacizumab in patients with unresectable and/or locally advanced or metastatic hepatocellular carcinoma.

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Background: IL-27 is a heterodimerized cytokine, a member of the IL-12/IL-23 cytokine family, and an immunoregulatory cytokine expressed by myeloid cells that dampens T and NK effector function. IL-27 is highly expressed by tumor-associated macrophages in several cancers, including hepatocellular carcinoma (HCC) and non-small cell lung cancer (NSCLC), and suppresses antitumor immune responses. Casdozokitug (Casdozo) is the only clinical-stage IL-27 targeting antibody and it increases IFN-g and T and NK cell activation in preclinical/clinical studies. A phase 1 study (NCT04374877) demonstrated a favorable safety profile and antitumor activity of casdozo as monotherapy and in combination with PD-1 blockade in indications, including HCC, with known high levels of IL-27 activation signature (Marron T, et al. *Ann Oncol*. 2023). A phase 3 study of toripalimab (tori) + bevacizumab (bev) demonstrated significant improvements in efficacy (overall survival [OS], progression-free survival [PFS], and objective response rate [ORR]) compared to sorafenib (Yinghong S, et al. CSCO 2024) in HCC. A phase 2 study of casdozo + atezolizumab + bev showed an acceptable safety profile and antitumor activity (ORR 38%, CR 17.2%, mPFS 8.1 mo) (Li D, et al. ASCO GI 2025). CHS-388-202 (NCT06679985) will evaluate the efficacy, safety, and biomarkers of tori + bev ± casdozo and optimize the dose for casdozo in combination with tori + bev as first-line treatment for patients (pts) with unresectable and/or locally advanced/metastatic HCC. **Methods:** CHS-388-202 is a Phase 2, open-label, randomized study and will enroll up to 72 pts randomized (1:1:1) to 1 of 3 treatment arms (IV Q3W): Arm A (tori 240 mg + bev 15 mg/kg + casdozo 700 mg), Arm B (tori 240 mg + bev 15 mg/kg + casdozo 1400 mg), Arm C (tori 240 mg + bev 15 mg/kg). Key eligibility criteria include treatment-naïve unresectable metastatic HCC with ≥1 measurable lesion; not suitable for surgical or local therapy; Child-Pugh A; ECOG PS 0 or 1; controlled hepatitis B virus or cured hepatitis C virus. Pts will be stratified by geographic region (Asia excluding Japan vs the rest of the world) and macrovascular invasion or extrahepatic spread of disease (presence vs absence). Primary endpoints are ORR by investigator review according to RECIST v1.1 and safety. Secondary endpoints are ORR by investigator review according to HCC modified RECIST (mRECIST) criteria; duration of response, PFS, and disease control rate by investigator review according to RECIST v1.1 and mRECIST criteria; OS, pharmacokinetics. A safety run-in evaluation will be conducted after the first ~6 pts are enrolled in Arms A and B, with ≥3 from each arm completing 1 cycle of treatment. Pts will remain on study treatment for ≤2 years or until documented disease progression or unacceptable toxicity. Enrollment is ongoing. Clinical trial information: NCT06679985. Research Sponsor: Coherus BioSciences.

TPS4218 **Poster Session**

A first-in-human study of MT-303, an innovative in vivo mRNA chimeric antigen receptor (CAR) therapy targeting GPC3, in adults with hepatocellular carcinoma.

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Background: Hepatocellular carcinoma (HCC) remains a leading cause of cancer mortality worldwide, with advanced cases posing significant treatment challenges. GPC3, a cell surface protein highly expressed in HCC, represents a promising therapeutic target. MT-303 is an in vivo chimeric antigen receptor (CAR) therapy, leveraging mRNA-lipid nanoparticle (LNP) technology to reprogram myeloid cells directly within the body. This novel platform eliminates the logistical and technical barriers of ex vivo CAR therapies while retaining the ability to activate targeted immune responses. MT-303's mRNA encodes a GPC3-targeted CAR receptor incorporating a single-chain variable fragment (scFv) linked to the transmembrane domain and cytoplasmic tail of CD89. Crucially, functional CAR expression is restricted to Fc receptor common gamma chain-expressing cells, predominantly myeloid cells, ensuring precise immune activation. Preclinical studies demonstrated that MT-303 effectively infiltrates tumors, triggers tumor cell killing, produces chemokines and cytokines, eliciting an adaptive antitumor immunity. Rodent models of "cold" tumors and nonhuman primate studies have highlighted MT-303's safety, pharmacodynamic effects, and dose-dependent activity, supporting its clinical development (Argueta, SITC 2024, #1125). **Methods:** This first-in-human, multicenter, open-label, Phase 1 dose-escalation trial evaluates the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary efficacy of MT-303 in participants with GPC3-expressing tumors, with a primary focus on Hepatocellular Carcinoma. MT-303 is administered intravenously every 14 days using a Bayesian Optimal Interval design, with backfill cohorts for dose refinement. The primary endpoints are safety, maximum tolerated dose (MTD), and recommended Phase 2 dose (RP2D). Secondary endpoints include detailed PK profiling and assessment of immune-related adverse events (e.g., ICANs, CRS). Exploratory endpoints encompass efficacy measures (e.g., objective response rate [ORR], duration of response [DOR]), immune reprogramming (e.g., peripheral CAR expression, cytokine profiles), and intratumoral immune changes, including T-cell receptor clonality and GPC3 modulation. Enrollment is ongoing, with safety and preliminary efficacy data expected to inform future development. Clinical trial information: NCT06478693. Research Sponsor: None.

TPS4219 Poster Session

A phase 1b/2, safety lead-in and dose-expansion trial of ivosidenib plus durvalumab and gemcitabine/cisplatin as first-line therapy in patients with locally advanced, unresectable or metastatic cholangiocarcinoma with an IDH1 mutation.

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Background: Cholangiocarcinomas (CCAs) are often advanced and incurable at the time of diagnosis. The phase 3 TOPAZ-1 trial showed improved OS and ORR with gemcitabine/cisplatin (GEM/CIS) and durvalumab (DURVA) vs GEM/CIS in unresectable advanced or metastatic biliary tract cancers. The phase 3 ClarIDHY trial demonstrated that the mIDH1 inhibitor ivosidenib (IVO) improved progression-free survival in CCA patients who have progressed from first or second-line chemotherapy and who have activating mutations in isocitrate dehydrogenase-1 (mIDH1). Additionally, mIDH1 suppresses key immune-related genes, with reversal of this effect when mIDH1 inhibitors are administered in preclinical CCA models. Finally, encouraging activity has been observed in treatment-naive mIDH1 patients administered with the mIDH1 inhibitor LY3410738 in combination with GEM/CIS. Given the ability of ivosidenib to stabilize advanced CCA, ability of IDH1 inhibition to restore immune activity, promising clinical activity of an mIDH1 inhibitor in combination with GEM/CIS, and the limited overlapping toxicities of these treatments, this study seeks to explore safety and preliminary activity of the quadruplet combination. **Methods:** This is a phase 1b/2, multicenter, safety lead-in and dose expansion, open-label study of IVO in combination with DURVA/GEM/CIS in first-line therapy of locally advanced, unresectable, or metastatic CCA with mIDH1. Treatment with up to one cycle of DURVA/GEM/CIS is permitted before initiation of study treatment. Key eligibility criteria include: a histopathological diagnosis; tumor mIDH1 based on local or centralized tissue testing (local testing by plasma ctDNA may be used); at least 1 measurable lesion as defined by RECIST v1.1; and adequate bone marrow, hepatic, and renal function. The study has a safety lead-in phase where IVO will be administered orally to the first 6 patients at a starting dose of 500 mg QD on every day of the 21-day cycle, plus DURVA 1500 mg IV infusion every 3 weeks for up to 8 cycles, plus GEM 1000 mg/m2 IV and CIS 25 mg/m2 IV on days 1 and 8 of each 21-day cycle, followed by IVO 500 mg QD and DURVA 1500 mg every 4 weeks of a 28-day cycle. Dose-limiting toxicities (DLTs) will be evaluated during the first cycle of quadruplet treatment. 6 additional patients may be enrolled to evaluate an alternative reduced dose of IVO 250 mg QD. The primary objective is to evaluate the safety and tolerability of the quadruplet combination, and to determine the recommended combination dose (RCD). The expansion phase will enroll approximately 40 patients who will be treated with the RCD, with the primary objective being to assess the clinical activity of the combination, as determined by a primary endpoint of confirmed complete or partial response using RECIST v1.1 criteria. Clinical trial information: NCT06501625. Research Sponsor: Servier.

TPS4220 **Poster Session**

A phase 2, randomized, multicenter study of adjuvant adebrelimab plus capecitabine in resected cholangiocarcinoma with high-risk factors: ACHIEVE.

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Background: Cholangiocarcinoma is a rare and aggressive group of gastrointestinal cancers. For early-stage disease following curative resection, capecitabine is a category 1 recommendation for adjuvant therapy for biliary tract cancer (BTC) according to the NCCN guidelines. However, recurrence rates remain high. For example, the BILCAP study reported a 5-year recurrence-free survival (RFS) rate of 34% with adjuvant capecitabine. Based on cholangiocarcinoma-specific cohort data from the Hepatobiliary Center, The First Affiliated Hospital of Nanjing Medical University, the 1-year RFS rate for intrahepatic cholangiocarcinoma (ICC) and hilar cholangiocarcinoma (HCCA) with high-risk factors is approximately 50% (unpublished data), highlighting a substantial unmet medical need. Immunotherapy has shown efficacy as adjuvant therapy in other cancer types. Results from the TOPAZ-1 and KEYNOTE-966 studies support the combination of immunotherapy and chemotherapy for advanced BTC, including locally advanced non-metastatic disease. Adebrelimab, a PD-L1 inhibitor, has shown promising results in several cancers. In China, it is approved for first-line treatment of extensive-stage small cell lung cancer with chemotherapy. The ACHIEVE study will assess the efficacy of adebrelimab plus standard adjuvant chemotherapy in ICC/HCCA patients after curative resection with high-risk factors. **Methods:** ACHIEVE is a Phase 2, randomized, open-label, multicenter study designed to assess the efficacy and tolerability of adebrelimab administered intravenously every three weeks for one year in combination with capecitabine (8 cycles) as adjuvant therapy for ICC or HCCA after curative resection. The study will enroll about 120 adult patients with histologically confirmed ICC or HCCA who have undergone complete resection (R0). Eligible participants must have an ECOG performance status of 0–1, confirmed complete response (CR) on imaging 4–8 weeks post-surgery, and at least one high-risk factor. High-risk factors are defined as follows: ICC: Single tumor $>$ 5 cm, multiple tumors, liver capsule breach, vascular invasion, regional lymph node metastasis; HCCA: Tumor invasion into surrounding tissues, vascular invasion, regional lymph node metastasis. Key exclusion criteria include locally advanced, unresectable, or metastatic disease at diagnosis and prior anti-cancer therapy before surgery. The primary endpoint is the 1-year recurrence-free survival rate (RFSR). Key secondary endpoints include overall survival (OS) and RFS, minimal residual disease (MRD), and patient-reported tolerability, and safety. Enrollment has begun, with six sites in mainland China participating. Clinical trial information: NCT06607276. Research Sponsor: None.

TPS4221 Poster Session

EMERALD-Y90: A phase 2 study to evaluate transarterial radioembolization (TARE) followed by durvalumab (D) and bevacizumab (B) for the treatment of participants (pts) with unresectable hepatocellular carcinoma (uHCC) eligible for embolization.

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Background: Locoregional therapy, such as transarterial chemoembolization (TACE) or TARE, is commonly used to treat uHCC eligible for embolization. Despite advances in TACE and TARE delivery, median progression-free survival (PFS) following treatment is <1 year, highlighting a need for new treatment options. EMERALD-1 (NCT03778957), a global phase 3 study, demonstrated a statistically significant improvement in PFS with TACE + D + B versus TACE + placebos in pts with uHCC eligible for embolization (hazard ratio, 0.77 [95% confidence interval, 0.61–0.98]; two-sided p-value = 0.032). With the increased use of TARE for patients with uHCC eligible for embolization in the US, a need exists for evidence to support additional treatment options in settings where TARE is preferred. The EMERALD-Y90 study will evaluate the efficacy and safety of TARE with D monotherapy, followed by D + B in pts with uHCC eligible for embolization. **Methods:** EMERALD-Y90 (NCT06040099) is a phase 2, single-arm study that will enroll ~100 pts aged ≥18 years with uHCC amenable to embolization who are ineligible for or have declined treatment with resection and/or ablation or liver transplant (transplant candidates are those listed for transplant or eligible to be listed and within Milan criteria). Eligible pts also must have Child-Pugh class A liver function and an Eastern Cooperative Oncology Group performance status of 0–1. Pts are allowed to receive a single TACE or TARE ≥6 months before the study or >1 TACE or TARE ≥12 months before the study. Prior TACE or TARE must have been administered for a different primary intrahepatic lesion unrelated to the current lesion, and pts should have a functional liver remnant $>30\%$. Exclusion criteria include prior systemic therapy, evidence of extrahepatic spread, or major portal vein invasion. Pts will receive partition-based dosing of TARE using Y-90 glass microspheres. Following TARE, pts will receive D 1500 mg (one dose) followed by D 1120 mg + B 15 mg/kg every 3 weeks until study completion or discontinuation criteria are met. The primary endpoint is PFS (time from start of TARE until date of disease progression [investigator (INV)-assessed per modified Response Evaluation Criteria in Solid Tumors (mRECIST)] or death due to any cause). Secondary endpoints include safety and tolerability, 6-, 12-, and 24-month PFS, objective response rate (percentage of pts with confirmed complete or partial response [INV-assessed per mRECIST]), overall survival (time from start of TARE until death due to any cause), and duration of response (time from date of first documented response until date of progression or death due to any cause). An early safety review is planned when approximately 15 pts have completed their first cycle of D + B dosing. Study enrollment is ongoing at 22 US sites. Clinical trial information: NCT06040099. Research Sponsor: AstraZeneca.

TPS4222 Poster Session

Trial in progress: A phase Ib/II study to evaluate the safety and efficacy of atezolizumab plus bevacizumab as adjuvant therapy following carbon ion radiotherapy in hepatocellular carcinoma (VANGUARD trial).

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Background: While hepatic resection remains the standard curative treatment for hepatocellular carcinoma (HCC), many cases are ineligible due to impaired liver function or patient-related factors. Percutaneous ablation is an option for small HCC but is limited by tumor size. Carbon ion radiotherapy (C-ion RT) has emerged as a promising modality, characterized by superior biological efficacy and dose distribution compared to conventional radiotherapy. Although HCC is relatively radiosensitive, conventional radiotherapy has limited efficacy due to low radiation tolerance of surrounding liver tissue. C-ion RT achieves effective treatment while minimizing radiation exposure through the superior dose localization of the carbon ion beam's Bragg peak. The establishment of adjuvant systemic therapy to prevent recurrence remains an urgent unmet need in HCC management. The IMbrave050 trial demonstrated the efficacy of combined atezolizumab and bevacizumab (Atezo+Bev) after resection or ablation, but recent analyses suggest diminishing long-term benefits. The combination of immune checkpoint inhibitors (ICIs) and radiotherapy has shown promise in several malignancies, with preclinical studies demonstrating synergistic enhancement of ICI efficacy through radiation-induced immunogenic cell death. Additionally, carbon ion radiation induces stronger immune responses compared to proton therapy. Based on these findings, we designed a phase Ib/II study to evaluate sequential C-ion RT followed by ICI as a novel therapeutic approach. **Methods:** This multicenter, open-label, single-arm phase Ib/II study evaluates the safety and efficacy of Atezo+Bev as adjuvant therapy following C-ion RT for HCC. Key inclusion criteria include treatment-naïve, Child-Pugh class A, maximum intrahepatic tumor diameter $\geq$4 cm and $\leq$3 intrahepatic tumors. After initial enrollment, patients undergo C-ion RT followed by a two-week observation period with eligibility screening for second enrollment. Eligible patients receive atezolizumab (1200 mg) and bevacizumab (15 mg/kg) every 3 weeks for up to 48 weeks, with radiological assessments every 3 months. The Phase Ib part will enroll six patients to evaluate dose-limiting toxicities. Secondary endpoints include adverse events (AEs) and serious AEs for safety and 1-year RFS, overall survival (OS) and 6-month OS rates for efficacy. If tolerability is confirmed, the trial will proceed to Phase II. Clinical trial information: jRCT2031240284. Research Sponsor: Chugai Pharmaceutical Co., Ltd.

TPS4223 **Poster Session**

Donafenib combined with capecitabine for postoperative adjuvant therapy of biliary malignant tumors with high risk of recurrence: A multi-center, randomized controlled, phase II study.

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Background: Biliary Tract Cancer (BTC) is an aggressive malignancy with rising incidence. Surgery is the only curative option, but only 10% of patients are eligible at diagnosis, and recurrence rates post-surgery can reach 67% within a year. The 5-year survival rate is only 5-15%. Emerging therapies, such as targeted and immunotherapies, show promise. A study combining GEMOX, tislelizumab, and donafenib (a tyrosine kinase inhibitor) in advanced BTC showed an 87.5% disease control rate (DCR) with strong safety and efficacy. The BILCAP study found that adjuvant capecitabine improved overall survival (OS) in resected BTC patients (median OS: 49.6 vs. 36.1 months; HR = 0.84). However, clinical research on adjuvant treatments for high-risk postoperative BTC remains limited, with no consensus on high-risk factors. This study evaluates the efficacy and safety of donafenib combined with capecitabine as adjuvant therapy for postoperative BTC with high recurrence. **Methods:** The study selected BTC patients prior to radical resection without any anti-tumor systemic therapy (including radiotherapy, chemotherapy, targeted therapy, immunotherapy) with at least one high-risk postoperative recurrence factors including specific stages according to the UICC/AJCC TNM 8th edition staging system: T_{2-4}, N_0, M_0 or T_{1-4}, N_1, M_0 (applicable to extrahepatic cholangiocarcinoma); T_{1b-4}, N_{0-1}, M_0 or T_{1a}, N_1, M_0 (applicable to intrahepatic cholangiocarcinoma), vascular invasion or neurophilic invasion as research subjects. Patients will be randomly divided into 1:1 groups. The experimental group consisted of donafenib (200mg, bid for 6 months) combined with capecitabine (1250mg/m^2, bid, treated for 2 weeks and stopped for 1 week, with 3 weeks as a treatment cycle, 8 cycles). The control group was capecitabine (same as experimental group). Treatment will start at least 4 weeks after radical resection and stop until patients experience disease recurrence or intolerable toxic side effects. The primary endpoint of the study was the 1-year recurrence free survival (RFS) rate. Secondary endpoints consisted of 2-year RFS, OS and safety assessment including incidence, severity, and relationship to study drugs of all adverse events (AEs), treatment-related adverse events (TRAEs), and serious adverse events (SAEs). Based on the data analysis of BTC cohort at our center, the 1y-RFS rate for the control group is set at 30%, while that for the experimental group is set at 60%. With a two-sided alpha of 0.05, a power of 0.80, and a randomization ratio of 1:1, the required number of RFS events is 64. Considering a 10% dropout rate, it is planned to enroll 35 participants per group, with a total planned enrollment of 70 participants. Dated by 20 January 2025, 8 of planned 70 patients have been enrolled. Clinical trial information: NCT06685289. Research Sponsor: None.

TPS4224 Poster Session

Australasian Gastro-Intestinal Trials Group (AGITG) STOPNET: A randomized study of cessation of somatostatin analogues (SSA) after peptide receptor radionuclide therapy (PRRT) in mid, hind-gut, and pancreatic neuroendocrine tumours.

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Background: PRRT is a standard therapeutic option for patients with metastatic well-differentiated somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours (GEP-NETs) following progression on SSA. It is uncertain whether current practice of continuing SSA after commencing PRRT is beneficial, especially in non-functioning NETs. Studies by Yordanova et al. (2018) and Sygula et al. (2022) have included heterogenous study populations and yielded conflicting results. **Methods:** STOPNET is a prospective, randomized, non-comparative, open-label, multi-center phase II trial led by the AGITG in collaboration with the Canadian Cancer Trials Group (CCTG) under the Commonwealth Neuroendocrine Tumor research collaborative (CommNETS). The trial aims to evaluate the outcomes of SSA cessation or continuation in patients with GEP-NETs undergoing PRRT after progression on SSA. The co-primary endpoints are 20-month PFS and feasibility for a phase III trial, assessed by recruitment over a 24-month period & patient acceptance of SSA cessation. Secondary endpoints include OS, rate of SSA recommencement, time to subsequent therapy, quality of life, cost-effectiveness and psycho-oncological impacts of SSA cessation. Eligible participants must have advanced or unresectable WHO grade 1/2 non-functioning GEP-NETs (excluding the foregut), and disease progression after receiving ≥3 months of SSA at standard growth-control doses. SSA must have been primarily commenced for growth control, as opposed to functional symptoms and for mid/hindgut NET's 24-hr urine 5-hydroxyindoleacetic acid must be < 1.5 times upper limit normal at screening. Participants will be randomized 2:1 to SSA cessation or continuation. SSA cessation arm will receive their last SSA ≥28 days prior to first PRRT, and the SSA continuation arm will continue SSA during and after PRRT. Following PRRT, participants will be assessed every 12 weeks (minimum 20 months) until disease progression or study closure, whichever occurs first. The sample size was calculated using Fleming's single stage design, assuming uninteresting and interesting 20-month PFS rates of 60% and 77% respectively. Novel translational research will be conducted to define and validate NET tissue and circulating biomarkers, with a particular focus on analysis of microRNA. Formalin-fixed paraffin-embedded (FFPE) tumor tissue will be retrieved (if available), with the collection of bloods at 3 time-points during study. The trial implemented the Australian Teletrial Program (ATP) to enhance equity of access for participants in regional, rural or remote locations. The trial will enroll 78 participants across 13 sites. Enrolment is open at 1 site in Australia & 4 sites in Canada, with 3 participants randomized as of Jan 2025. Clinical trial information: NCT06345079. Research Sponsor: Medical Research Future Fund (MRFF); Tour de Cure; AGITG philanthropic funding; Canadian Neuroendocrine Tumour Society (CNETS); Canadian Institutes of Health Research (CIHR).

TPS4225 Poster Session

A multi-centre, stratified, open, randomized, comparator-controlled, parallel group phase II trial comparing adjuvant treatment with 177Lu-DOTATATE to standard of care in patients after resection of neuroendocrine liver metastases (NELMAS).

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Background: Gastro-entero-pancreatic (GEP) neuroendocrine tumours (NET) are steadily increasing in incidence and prevalence. About 65%-95% of GEP NET show hepatic metastases. Surgery is the mainstay of treatment for NE LM. While macroscopically complete resection for NE LM is associated with favourable overall survival (OS), recurrence rates of up to 70% at 3 years and up to 95% at 5 years are reported. These results call for adjuvant treatment concepts which have not yet been established. **Methods:** A prospective open-label, multicentre randomised parallel-group trial was conducted in patients with resected GEP NE LM. Adjuvant treatment with ^{177}Lu-DOTA^{0}-Ty^{3}-ocreotate (^{177}Lu-DOTATATE) (total administered activity 14.8 GBq) is compared with standard of care (SOC). The frequency of administration is 2 cycles (8±1weeks between each cycle). The first cycle is applied 8±2 weeks after liver resection. The control arm consists of SOC. Main inclusion criteria are well differentiated grade 1 or grade 2 (Ki67 < 20%) GEP NET, R0 or R1 resection of NE LM, primary tumour already resected or resected synchronously with LM, ^{68}Ga DOTATATE PET/CT prior to surgery confirming LM and no extrahepatic disease (except resectable perihilar lymph node involvement and/or primary tumour, if still in place). Main exclusion criteria are high grade NET, neuroendocrine carcinoma, R2 resection of LM, peptide receptor radionuclide therapy at any time prior to randomisation in the study, and any type of liver directed therapy within 12 weeks prior to randomisation in the study. Primary endpoint are disease-free survival (DFS) at 3 years after liver resection. The sample size of 106 patients in total is powered to detect an HR of 0.27, reflecting a 44% DFS probability at 3 years post-surgery in the ^{177}Lu-DOTATATE arm compared with a 25% in the SOC arm. Secondary endpoints OS, time to tumour recurrence, time to administration of subsequent antineoplastic therapy, safety and tolerability of ^{177}Lu-DOTATATE, health-related quality of life, patient reported outcomes, and cost effectiveness. Ancillary objectives explore the clinical utility of novel molecular based biomarkers in identification of residual microscopic disease and early detection of recurrent disease. Enrolment has begun. Follow-up data will be collected for 5 years overall from the date of randomisation of the last patient. Discussion: The NELMAS trial aims to investigate the efficacy of adjuvant therapy with ^{177}Lu-DOTATATE (2 cycles) compared to standard of care in preventing tumour recurrence in patients following R0/R1 resection of LM of well differentiated GEP NET. Clinical trial information: NCT05987176. Research Sponsor: Novartis/AAA; The Taylor Family 2010 Charitable Trust.

TPS4226 Poster Session

NCI 10479: A phase I dose escalation-expansion trial of sunitinib malate plus lutetium (Lu-177) dotatate in somatostatin receptor positive pancreatic neuroendocrine tumors.

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Background: Patients with metastatic or unresectable pancreatic neuroendocrine tumors (PanNETs) have a poor prognosis, even with currently available treatments, with a 5-year overall survival (OS) of less than 20%. Lutetium Dotatate (Lu-177) is a radiopharmaceutical that consists of the somatostatin analogue DOTA-Tyr3-Octreotate, coupled to the metal-ion chelating moiety, DOTA, and radiolabeled with lutetium-177. Lu-177 was approved by the FDA in 2018 for treatment of somatostatin receptor (SSTR)-positive gastroenterohepatic NETs, but it is limited in its efficacy to achieve cytoreduction and provide durable responses. Sunitinib malate is an oral small-molecule tyrosine kinase inhibitor targeting VEGFRs, PDGFRs, and KIT and is also FDA approved as a monotherapy for the treatment of metastatic unresectable PanNETs. There is preclinical, as well as clinical evidence of sunitinib being used as a radiosensitizer with classic radiation, but it has never been combined with a radiolabeled analogue in patients with PanNETs. **Methods:** This is a Phase I dose escalation/expansion study aiming to enroll up to 24 patients across several sites. Eligible patients will be offered fixed dose Lu-177 at 200 mCi for 4 fractions with concurrent oral sunitinib administration initiating on C1D1 and concluding 28 days after the last Lu-177 infusion. Dose escalation applies to sunitinib and will be guided by a 3+3 design to determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D). Once the RP2D has been established, up to 12 more patients will be offered participation in the expansion phase in an attempt to further record antitumor activity and correlation with imaging, tumor markers, as well as Lu-177 dosimetry. Treatment will continue until disease recurrence/progression, unacceptable toxicity, or completion of planned protocol. Key eligibility criteria include age $>=$ 18 years, ECOG performance status $<=$ 2, histologic diagnosis of metastatic, unresectable well- or moderately-differentiated SSTR-positive PanNETs of any grade, up to 1 prior treatment except for somatostatin analogues and appropriate baseline hematological parameters. Key exclusion criteria are prior use of sunitinib, Lu-177 or other radiopharmaceuticals, myocardial or cerebrovascular accident within the prior 12 months and left ventricular ejection fraction of $<=$ 50%. The study uses an 8-week safety window to determine its primary endpoint, which is DLTs during administration of the combination. Secondary endpoints are objective response (ORR), duration of response (DOR), progression-free survival (PFS) and overall survival (OS), intensity of tumor uptake on pre-treatment SSTR PET and post Lu-177, chromogranin A level response as well as optional dosimetry imaging. Enrollment is ongoing. Clinical trial information: NCT05687123. Research Sponsor: National Cancer Institute.

TPS4227 Poster Session

An open-label, dose-finding, phase Ib study to assess the safety, tolerability of nesuparib (JPI-547), a dual inhibitor of PARP/TNKS, in combination with modified FOLFIRINOX (mFOLFIRINOX) and gemcitabine-nab-paclitaxel (GemAbraxane) in patients with locally advanced and metastatic pancreatic cancer.

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Background: Pancreatic ductal adenocarcinoma (PDAC) is a leading cause of cancer deaths, with most cases diagnosed at advanced stages. Current maintenance therapy with the PARP inhibitor, olaparib, benefits only patients with germline BRCA1/2 mutations (Approximately 5-7 % of PDAC cases). However, homologous recombination deficiency (HRD)-related mutations occur in ~15% of PDACs, potentially expanding the utility of PARP inhibitors. Nesuparib, a next-generation PARP inhibitor, also targets tankyrase, disrupting WNT and Hippo signaling pathways which are critical for homologous recombination repair. This dual mechanism mimics BRCA loss (''BRCAness''), sensitizing HRD-positive tumors without BRCA mutations to PARP inhibition, broadening therapeutic options. Combining PARP inhibitors with chemotherapy (e.g., irinotecan or platinum-based drugs) enhances sensitivity to DNA damage. Preclinical studies showed nesuparib inhibited tumor growth as monotherapy and achieved higher efficacy in combination with standard treatments. In a prior phase I trial, nesuparib showed promising antitumor activity, with overall response rate of 28.2% and disease control rate of 64.1%. This Phase Ib study aims to evaluate the efficacy of nesuparib in combination with standard chemotherapy for advanced PDAC using a 3+3 dose-escalation design. **Methods:** This multicenter, open-label, Phase Ib, dose-finding study will enroll 24–48 patients with locally advanced or metastatic PDAC. Two arms are included: Arm A (mFOLFIRINOX combination) and Arm B (GemAbraxane combination), each with 12–24 subjects across four dose groups (3–6 patients per group). Nesuparib is administered orally under fasting conditions ranging from Dose Levels -2 (12.5 mg qd) to 4 (100 mg qd), starting at Dose Level 1 (25 mg qd) with a 5 days on/2 days off schedule. Based on the occurrence of dose-limiting toxicities (DLTs), the dose may be escalated to higher levels (Dose Levels 2, 3, or 4) or reduced to lower levels (Dose Levels -1 or -2) with a 5 days on/2 days off or 3 days on/4 days off schedule. Arm A includes mFOLFIRINOX chemotherapy with biweekly oxaliplatin (65 mg/m^2), leucovorin (400 mg/m^2), irinotecan (135 mg/m^2), and 5-FU (2,400 mg/m^2). Arm B involves gemcitabine (1,000 mg/m^2) and nab-paclitaxel (125 mg/m^2) on Days 1, 8, and 15 of a 28-day cycle. Primary objectives are to determine the maximum tolerable dose (MTD) and recommended Phase II dose (RP2D) and to identify the optimal combination regimen based on safety. Secondary objectives include evaluating safety and antitumor activity. Enrollment began in Q1 2022. ClinicalTrials.gov ID: NCT05257993. Clinical trial information: NCT05257993. Research Sponsor: Onconic Therapeutics.

TPS4228 **Poster Session**

ALTER-PA001: A multicenter, randomized study of anlotinib and benmelstobart in combination with AG chemotherapy vs. AG as first-line treatment for metastatic pancreatic cancer.

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Background: Metastatic pancreatic cancer (mPC) remains one of the most challenging malignancies to treat, with limited effective therapeutic options. While AG chemotherapy (nab-paclitaxel and gemcitabine) is a current standard first-line regimen, new combinations are needed to improve outcomes. Preclinical data suggest potential synergistic effects of anlotinib, a multi-target tyrosine kinase inhibitor, and benmelstobart, a novel anti-PD-L1 antibody, with chemotherapy. This study aims to evaluate the efficacy and safety of this combination in mPC. **Methods:** ALTER-PA-001 is a multicenter, open-label, randomized, controlled phase 2 trial that compared anlotinib plus benmelstobart and AG with AG in patients with treatment-naïve mPC. Eligible patients are aged 18-75, ECOG 0-1, with histologically or cytologically confirmed PC. A total of 104 patients will be randomly assigned in a 2:1 ratio to receive anlotinib (8 mg orally, QD, d1–14), benmelstobart (1200 mg IV, d1), nab-paclitaxel (125 mg/m^2 IV, d1, d8), and gemcitabine (1000 mg/m^2 IV, d1, d8) every 21 days or AG regimen with nab-paclitaxel and gemcitabine at the same doses and schedule. The randomisation is done centrally and stratified by the presence of liver metastasis. Patients achieving CR, PR, or SD after 8 cycles will enter a maintenance phase with continued treatment based on their assigned arm. Tumor assessment is performed every 6 weeks for induction treatment, and every 9 weeks for maintenance phase. The primary endpoint is objective response rate (ORR), with secondary endpoints including progression-free survival (PFS), disease control rate (DCR), duration of response (DoR), overall survival (OS), and safety. Exploratory biomarker analyses will assess correlations between baseline tumor characteristics and therapeutic outcomes. This trial is actively recruiting in November 2024. Clinical trial information: NCT06621095. Research Sponsor: None.

TPS4229 **Poster Session**

A phase 1b/2 trial of onvansertib in combination with NALIRIFOX for first line treatment of advanced pancreatic cancer (PANCONVA trial).

Anup Kasi, Raed Moh'd Taiseer Al-Rajabi, Fairooz F. Kabbinavar, Nancy Sherman, Haoran Li, Milind A. Phadnis, Shannon Bradbury, Cathey Belcher, Jordan Rose, Ramanand Arun Subramanian, Manidhar Reddy Lekkala, Timothy Schmitt, Sean Kumer, Clay King, Mojtaba Olyaee, Amit Rastogi, Reza Hejazi, Joaquina Celebre Baranda, Weijing Sun; University of Kansas Cancer Center, Fairway, KS; University of Kansas Cancer Center, Kansas City, KS; Pharma, Los Angeles, CA; Cardiff Oncology, Inc., San Diego, CA; University of Kansas Cancer Center, Westwood, KS; Department of Biostatistics & Data Science, University of Kansas Medical Center, Kansas City, KS; University of Kansas Cancer Center UKH - Southwest Office, Topeka, KS; University of Kansas Medical Center, Kansas City, KS; University of Kansas Medical Center (KUMC), Kansas City, KS; University of Kansas, Kansas City, KS; University of Kansas Medical Center, Department of Internal Medicine, Kansas City, KS; Department of Medical Oncology, University of Kansas Cancer Center, Westwood, KS

Background: Pancreatic cancer is a highly lethal disease. Despite research and drug development efforts focused on KRAS, no effective RAS inhibitors have been approved for the treatment of pancreatic cancer with KRAS mutation. PLK1 inhibition is a potential target in KRAS-mutated pancreatic cancer and may provide a new first-line treatment option. Onvansertib (also known as PCM-075 and NMS-1286937) is the first PLK1-specific adenosine triphosphate competitive inhibitor administered by oral route to enter clinical trials with proven antitumor activity in different preclinical models. **Methods:** This is a phase 1b/II, non-randomized, open label single arm study being conducted at the University of Kansas Cancer Center and its affiliated sites. The study is open for enrollment. Eligibility: Key inclusion includes pts with locally advanced, unresectable, or metastatic pancreatic adenocarcinoma who are treatment naïve, have adequate archival tissue for biomarker evaluation or are willing to undergo a biopsy, and have an ECOG of 0-1. Key Exclusion: Planned concomitant use of medications known to prolong the QT/QTc interval, use of strong CYP3A4 or CYP2C19 inhibitors or strong CYP3A4 inducers. Treatment Plan: The phase 1b (safety lead-in) will follow a dose de-escalation phase in which up to 2 different Onvansertib dose levels will be tested in combination with standard NALIRIFOX. Onvansertib starting dose level is 30mg orally once daily. The Phase II portion of the study will be a single-arm open-label enrollment with dosing based on the starting dose determination in the Phase Ib portion of the study (30mg or 20mg). NALIRIFOX (Nano-liposomal Irinotecan 50 mg/m2, Oxaliplatin 60 mg/m2, Leucovorin 400 mg/m2, 5-FU 2400 mg/m2) will be administered intravenously on D1 of the 14-day cycle. Onvansertib will be dosed orally on D1-5 of each 14-day cycle. Imaging will be performed at baseline and after every 4 cycles. Objectives: The primary objective of this study is to determine anti-tumor activity by measuring Overall Response Rate (ORR). The secondary objectives are to determine treatment safety based on toxicities in participants who have received at least one dose of onvansertib, to determine anti-tumor activity by Progression Free Survival (PFS), to determine anti-tumor activity by Disease Control Rate (DCR), to determine Overall Survival (OS). Statistical Plan: Simon's two-stage Optimum design will be used. The null hypothesis that the true response rate is 41% will be tested against a one-sided alternative that the true response rate is 65%. In the first stage, 10 evaluable pts will be enrolled. If there are 4 or fewer responses in these 10 pts, the study will be stopped. Otherwise, 11 additional evaluable pts will be accrued for a total of 21 evaluable pts. The null hypothesis will be rejected if 12 or more responses are observed in 21 evaluable pts. Clinical trial information: NCT06736717. Research Sponsor: Cardiff Oncology.

TPS4230 Poster Session

Trial in progress: RASolute 302—A phase 3, multicenter, global, open-label, randomized study of daraxonrasib (RMC-6236), a RAS(ON) multi-selective inhibitor, versus standard of care chemotherapy in patients with previously treated metastatic pancreatic ductal adenocarcinoma (PDAC).

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Background: Patients with previously treated metastatic PDAC have significant need for treatments with improved efficacy and tolerability. RAS is an oncogenic driver in > 90% of patients with PDAC. Daraxonrasib (RMC-6236) is an oral, RAS(ON) multi-selective, tri-complex inhibitor of GTP-bound mutant and wild-type RAS. In the ongoing Phase 1 monotherapy trial (NCT05379985), daraxonrasib exhibited a manageable safety profile with primarily low-grade rash and GI toxicities, and encouraging ORR, PFS and OS in a broad population of previously treated patients with RAS mutant metastatic PDAC (J Clin Oncol 43, 2025 [suppl 4; abstr 722]). The significant unmet need for alternative treatment options, along with the preliminary clinical data of daraxonrasib monotherapy, support its evaluation in the ongoing Phase 3 clinical trial, RASolute 302, in patients with previously treated metastatic PDAC. **Methods:** RASolute 302 is a global, multicenter, open-label, randomized study (NCT06625320) designed to evaluate daraxonrasib outcomes compared to investigator's choice of standard of care chemotherapy as a 2L treatment in patients with metastatic PDAC. Eligibility includes patients ≥18 years old, ECOG performance status 0 or 1, disease progression on 1 prior line of either a 5-fluorouracil or gemcitabine-based regimen in the metastatic setting, and documented RAS mutation status (mutant or wild-type). Eligible RAS mutations are defined as nonsynonymous mutations in KRAS, NRAS, or HRAS at codons 12, 13, or 61 (G12, G13, or Q61). Patients with tumors that are RAS wild-type and received appropriate approved targeted therapy for actionable mutations are also eligible. A 1:1 randomization of approximately 460 patients will receive daraxonrasib 300 mg daily or investigator's choice of chemotherapy (gemcitabine/nab-paclitaxel, mFOLFIRINOX, nal-IRI/5-FU/LV, or FOLFOX) until unacceptable toxicity or disease progression. For patients randomized to daraxonrasib, recommended prophylactic measures for rash include oral antibiotics and topical corticosteroids. Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) tumor assessments will be performed every 8 weeks until disease progression, withdrawal of consent, lost to follow up, or death, whichever occurs first. Dual primary endpoints are progression-free survival (PFS) as assessed by blinded independent central review and overall survival (OS) in the RAS G12X-mutant population. Key secondary endpoints include PFS, OS, objective response and quality of life measures in the all-patient population with tumors carrying RAS mutations (G12X, G13X or Q61X) or RAS wild-type. Enrollment for the trial commenced in October 2024. Clinical trial information: NCT06625320. Research Sponsor: Revolution Medicines, Inc.

TPS4231 Poster Session

A phase 2 study of botensilimab and AGEN1423, an anti-CD73-TGFβ-trap bifunctional antibody, with or without chemotherapy in subjects with advanced pancreatic cancer.

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Background: Traditional immune checkpoint inhibitors have shown limited benefit in pancreatic ductal adenocarcinoma (PDAC) owing to non-redundant immune resistance mechanisms dominating the tumor microenvironment (TME). Transforming growth factor (TGF)-β and cluster of differentiation (CD)73-adenosine represent two major immunoregulatory and pro-tumorigenic pathways responsible for therapeutic resistance and progressive disease in PDAC. AGEN1423 (also known as dalutrafusp alfa and GS-1423) is a bifunctional, humanized, aglycosylated immunoglobulin G1 kappa antibody that selectively inhibits CD73-adenosine production and neutralizes active TGF-β signaling. Botensilimab (BOT) is an Fc-enhanced multifunctional anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibody. We hypothesize that the combination of AGEN1423 with BOT can rescue T-cell functional activity leading to responses in advanced PDAC. **Methods:** An investigator-initiated open label Phase 2 study to evaluate the safety, tolerability, and initial efficacy of BOT + AGEN1423 +/- chemotherapy in patients with metastatic PDAC (NCT05632328). In cohort 1, 12 patients with metastatic PDAC with disease progression to at least one line of treatment will receive AGEN1423 30mg/kg IV Q2W for 4 doses + BOT 150mg IV Q6W ongoing for up to 2 years. If the combination is considered safe and tolerable, and objective response is achieved in at least 1 subject, the study will proceed to Cohort 2. In Cohort 2, 12 additional patients with disease progression on first-line fluorouracil-based chemotherapy will be enrolled to receive second-line gemcitabine and nab-paclitaxel in combination with AGEN1423 30mg/kg IV Q2W for 4 doses + BOT 150mg IV Q6W. Key eligibility criteria include histologically or cytologically confirmed metastatic pancreatic adenocarcinoma, age ≥18 years, Eastern Cooperative Oncology Group (ECOG) performance status ≤1, adequate organ function, and measurable disease by RECISTv1.1. A pre-treatment and on-treatment tumor biopsy will be obtained for translational studies. The primary endpoint is to estimate the objective response rate (ORR) according to RECISTv1.1 criteria. Secondary endpoints include safety and tolerability as defined by the incidence of AEs as assessed according to CTCAE v5, disease control rate (DCR), progression-free survival (PFS), and overall survival (OS). Translational endpoints include the characterization of the transcriptional signatures in paired biopsies obtained before and on-treatment with BOT + AGEN1423, as well as the changes in cell composition of the TME following treatment using multiplexed immunofluorescence spatial technology. Enrolment has started and accrual is anticipated to complete in Q4 2025. Clinical trial information: NCT05632328. Research Sponsor: Agenus, Inc.

TPS4232 **Poster Session**

Adaptive organoid-based precision therapy study in pancreatic cancer (ADOPT): A phase II single-arm study to evaluate the efficacy of patient-derived organoid (PDO)-directed therapy in advanced pancreatic ductal adenocarcinoma (PDAC).

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Background: PDAC is a devastating malignancy. High-throughput genomic technologies have yielded insights regarding the molecular underpinnings and heterogeneity of PDAC. Systemic treatment options are limited to cytotoxic chemotherapies, except for approx. 10%, who receive targeted treatment based on genomic profiling. PDO's are three-dimensional *ex vivo* experimental models grown directly from tumor tissue and can provide a direct assessment of drug response. By directly exposing cancer cells to potential drug therapies, functional profiling provides a dynamic measurement of response that is more informative than static gene panels. PDOs can theoretically be used to direct therapeutic decisions, offering an opportunity to expand the reach of precision therapies for PDAC beyond genomics. To date, PDO testing has been limited by small sample sizes, few drugs included in the screens, and retrospective studies. To expand the impact of precision therapy, we developed a rapid high-throughput screening (HTS) platform where over 3,000 drugs can be tested in PDOs within 8-10 weeks of diagnosis. In ADOPT, we aim to formally investigate the efficacy of PDO-directed therapy in a prospective phase II study, leveraging our existing platforms using real-time HTS of PDOs. This study represents one of the first formal trials of PDO-directed therapy in solid tumors. Our novel approach will enroll pts with advanced PDAC who do not have alternative treatment options.
Methods: This is an actively recruiting prospective, single-arm phase II trial. Patients (pts) with advanced epithelial PDAC are eligible if they either: 1) progressed on, were intolerant to, or refused first-line or subsequent therapies (Cohort A), or 2) have stable disease after $\geq$8 cycles of FOLFIRINOX ("Maintenance" Cohort B) and have a PDO showing sensitivity to an approved HC drug. Pts will be recruited, from multiple ongoing studies including PROSPER-PANC where we have successfully generated and tested a PDO. PDO-directed treatment will be selected based on drug sensitivity as tested through our validated HTS platform. Each case will be discussed at our PDO dedicated tumor board. All pts must meet the inclusion/exclusion and drug-specific eligibility criteria. The primary endpoint is disease control rate. A Simon's two-stage optimal design will be used to test the hypothesis: H0: $P \leq 0.05$ versus H1: $P \geq 0.25$. In the first stage, 9 pts will be evaluated. The trial will be discontinued if no disease control response is observed in this stage. If at least one response is observed, then the trial will continue to the second stage and an additional 17 pts will be evaluated for a total of 26 evaluable. This design has a one-sided alpha of 0.05 and power of 80%. We will reject the null hypothesis after 26 if 3 or more responses are observed. Clinical trial information: awaited. Research Sponsor: Ontario Institute for Cancer Research and Princess Margaret Cancer Foundation; Terry Fox Research Institute - Marathon of Hope Cancer Centres Network Funding; Sinai Health Foundation; The MNitz Pancreatic Cancer Research Fund (Michelle Reisman); The MNitz Pancreatic Cancer Research Fund (Veroli Cultural Society); The MNitz Pancreatic Cancer Research Fund (Elyse Graff).

TPS4233 Poster Session

Phase I trial of MK2 inhibitor in combination with mFOLFIRINOX for untreated metastatic pancreatic ductal adenocarcinoma.

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Background: Zunsemetinib (also known as ATI-450) is an investigational small molecule inhibitor targeting MAPK-Activated Protein Kinase (MAPKAPK2, or MK2). Preclinical work conducted by the Lim Lab at Washington University in St. Louis demonstrated that FOLFIRINOX activates heat shock protein 27 (Hsp27), a molecule with pleiotropic pro-survival properties, and beclin1, a key mediator of autophagy, in pancreatic ductal adenocarcinoma (PDAC) models. In an autochthonous PDAC (KPC) mouse model, zunsemetinib synergized with FOLFIRINOX, resulting in near-complete ablation of all PDAC foci and significantly improved mouse survival. Additionally, mice treated with zunsemetinib experienced significantly less intestinal damage and weight loss—common concerns associated with FOLFIRINOX. These preclinical data support the rationale for combining zunsemetinib with FOLFIRINOX in PDAC patients. **Methods:** We are conducting a phase I, single-arm, open-label study of zunsemetinib in combination with mFOLFIRINOX in patients with untreated metastatic PDAC. The study consists of two phases: a dose escalation phase and an expansion phase. During the dose escalation phase, zunsemetinib dosing will proceed according to the BOIN design with a cohort size of 3. A total of 6–21 patients will be enrolled at Washington University. Patients will receive zunsemetinib starting at Dose Level 1 (40 mg twice daily), with dose escalation continuing until the recommended phase 2 dose (RP2D) is determined. Patients will remain in the study until disease progression or treatment intolerance. In the expansion phase, up to 30 additional patients will be enrolled to further assess the toxicity profile of zunsemetinib in combination with mFOLFIRINOX. These patients will begin at the RP2D and continue on study treatment until disease progression or treatment intolerance. Eligible patients must be treatment-naïve, newly diagnosed, and have histologically or cytologically confirmed PDAC for which mFOLFIRINOX is deemed a suitable treatment option. The primary objective is to determine the dose-limiting toxicities (DLTs) and RP2D of zunsemetinib in combination with mFOLFIRINOX. Secondary objectives include assessing toxicity profiles, progression-free survival (PFS) at six months and overall PFS, disease control rate, overall response rate, overall survival, CA 19-9 response at the RP2D, and pharmacokinetics of zunsemetinib in PDAC treated with mFOLFIRINOX. Exploratory objectives include evaluating pharmacodynamic markers via immunohistochemistry (e.g., phospho-Hsp27 to assess pharmacodynamics of zunsemetinib, LC3B to assess autophagy, and TUNEL staining to evaluate DNA damage) and analyzing pathway suppression through RNA sequencing. Pre- and post-treatment serum samples will also be collected for the analysis of inflammatory cytokines. Clinical Trial Registration: NCT06648434. Clinical trial information: NCT06648434. Research Sponsor: Pancreatic SPORE (P50 CA272213); Aclaris.

TPS4234 Poster Session

An open-label, phase 1 trial with expansion cohort of botensilimab (AGEN1181) + balstilimab (AGEN2034) + nab-paclitaxel + gemcitabine + cisplatin + chloroquine + celecoxib in adult patients with previously untreated metastatic pancreatic cancer.

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Background: The unfolded protein response (UPR) is an adaptive endoplasmic reticulum (ER) stress pathway that and can prevent cellular death under moderate stress conditions or promote apoptosis under severe stress. The UPR is often upregulated in pancreatic cancer cells and has been identified as a promising target for therapeutic intervention. We hypothesize that inducing severe ER stress by combining multiple chemo and immunotherapy agents will cause pancreatic cancer cells to enter the apoptotic UPR pathway, destroying these cells and improving patient survival. Prolonged ER stress is achieved in this study by using chemotherapy (nab-paclitaxel + gemcitabine + cisplatin) in combination with 2 immunotherapy agents: botensilimab (AGEN1181), an Fc-engineered anti-CTLA-4 monoclonal antibody, and balstilimab (AGEN2034), a human monoclonal immunoglobulin (Ig) G4 (IgG4) antibody designed to block programmed cell death protein (PD-1) binding by PD-L1 and PD-L2. Additionally, 2 agents are included to help block apoptosis escape routes: chloroquine to inhibit autophagy and celecoxib to reduce tumor microenvironment inflammation. **Methods:** This single-center, open-label, phase 1 study evaluates the safety, tolerability, and preliminary efficacy of two botensilimab doses in combination with fixed doses of balstilimab (240 mg) + nab-paclitaxel (125 mg/m^2) + gemcitabine (1000 mg/m^2) + cisplatin (25 mg/m^2) + chloroquine (500 mg) + celecoxib (200 mg) in adult patients with previously untreated metastatic pancreatic cancer (NCT06076837). The study design consists of 6 patients in a dose 1 cohort at 50 mg botensilimab + combination regimen and an escalated dose 2 cohort of 6 patients at 75 mg botensilimab + combination regimen (pending dose 1 cohort safety signals), with an additional 6 patients in an expansion cohort treated at the determined maximum tolerated dose (MTD) of botensilimab (Total N = 18). Adverse events (AEs) are evaluated according to NCI CTCAE v5.0 and tumor response is assessed by RECIST v1.1. Key eligibility criteria include 1) histologically confirmed diagnosis of metastatic pancreatic ductal adenocarcinoma with measurable disease on baseline imaging, 2) life expectancy of at least 3 months, 3) no previous radiotherapy, surgery, chemotherapy, or investigational therapy for the treatment of metastatic disease, and 4) no prior immune checkpoint inhibitor therapy. Enrollment began in January 2025 at the HonorHealth Research Institute. Clinical trial information: NCT06076837. Research Sponsor: TGen Foundation; Purple Pansies Foundation.

TPS4235 **Poster Session**

A supervised prehabilitation program for patients with pancreatic cancer.

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Background: Individuals who develop pancreatic cancer tend to be older, with 70% of pancreatic diagnoses occurring in those ≥ 65 years (2). Older patients are at increased risk for sarcopenia which is the progressive loss of skeletal muscle mass, tone, quality and strength and has been reported to affect 65% of pancreatic cancer patients (4). PREHAB is the process of improving the functional capability and psychological health of the individual to reduce the incidence and/or severity of future impairments (6). The foundation of PREHAB is functional exercise although components of nutrition and stress reduction may be included (9). PREHAB sessions are typically delivered through structured programs and have been shown to have a number of benefits such as improvements in functional activity and decreased postoperative complications (8). In a study by Ngo-Huang et al, 50 pancreatic cancer participants participated in a home-based multimodal program resulting in improved physical function and health related quality of life (15). Given the numerous benefits, the purpose of this study is to demonstrate the feasibility of a multimodal supervised PREHAB program in pancreatic cancer patients which we believe could have greater benefits than unsupervised programs. **Methods:** This is a single arm pilot study assessing the feasibility of a supervised prehabilitation program for patients with pancreatic cancer. Inclusion criteria include a diagnosis of any stage pancreatic cancer, independence with ambulation, and a lower level of physical activity as assessed by the Godin-Shepard Leisure-Time Physical Activity Questionnaire. To our knowledge, this is the first study in which all exercises sessions are in-person and supervised by exercise technicians in pancreatic cancer. Additionally, while prehabilitation typically takes place during the neo-adjuvant therapy period, this study will also include patients with metastatic disease on continuous chemotherapy. Participants will undergo baseline evaluations testing strength, endurance, balance, subjective measures and sarcopenia measures. This will be immediately followed by one-hour long supervised exercise sessions 3x per week for 6 weeks in which participants will engage in aerobic training and resistance training targeting major muscle groups. Following the intevention, measures will be collected immediately afterwards and at 3 month follow-up. The primary analysis will test the hypothesis of feasibility using an one-sided exact Binomial test at 25% significance level. If 10 or more patients attend a minimum of 60% of exercise sessions during the initial 6-week period, then the study will be declared feasible. 11 of 16 patients have been enrolled to date. Clinical trial information: NCT05692323. Research Sponsor: Cedars Sinai Medical Center (Internal Funding).

TPS4236 Poster Session

IMMUNORARE[5]: A national platform of 5 academic phase II trials coordinated by Lyon University Hospital to assess the safety and the efficacy of the immunotherapy with domvanalimab + zimberelimab combination in patients with advanced rare cancers—The Peritoneal Mesotheliomas Cohort.

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Background: In patients with rare cancers, there is an unmet medical need for investigating innovative therapeutics beyond standard first-line treatment. Indeed, these diseases are rarely assessed in clinical trials. The standard 1st-line treatment of peritoneal mesothelioma relies on platinum and pemetrexed, with no validated 2nd-line treatment so far. Several studies suggested that immunotherapy, such as ipilimumab + nivolumab or atezolizumab + bevacizumab, is active in this disease. There is a strong biological rationale for concurrent blockage of TIGIT and PD1 pathways in mesothelioma. **Methods:** IMMUNORARE[5] (NCT06790706) is a platform of 5 single arm phase II trials testing the safety and the efficacy of DOMVANALIMAB (anti-TIGIT) and ZIMBERELIMAB (anti PD-1) in 5 independent cohorts of rare cancers. The trial, sponsored by Lyon University Hospital, is conducted in 15 French centers, in partnership with the corresponding national networks of reference centers. The PERITONEAL MESOTHELIOMA cohort, led in collaboration with the RENAPE network (https://www.renape-online.fr/), will enroll 27 patients in progression after at least 1 line of platinum + pemetrexed based-chemotherapy regimen, with evaluable lesions at the baseline (modified RECIST criteria). Patients previously treated with immunotherapy will not be eligible. Patients will receive intra-venous DOMVANALIMAB and ZIMBERELIMAB, every three weeks, until disease progression. The primary endpoint will be the progression-free survival rate at 6 months. The disease progression (clinical or radiological) will be confirmed by the RENAPE experts. The secondary endpoints are tolerance, overall response rate and duration of response, progression-free and overall survival. A two-stage Simon design was used, with early termination rules for futility (5% one-sided alpha level, 80% power). The treatment would be considered interesting if the percentage of patients free from disease progression at 6-months is statistically higher than 35%; 60% is expected. Translational research projects will be developed aiming at deciphering cellular and molecular mechanisms involved in response to treatment. Moreover, data from the prospectively-maintained RENAPE database will be investigated to build a synthetic historical arm representative of the efficacy of the standard treatments in a similar population of patients. Clinical trial information: NCT06790706. Research Sponsor: GILEAD.